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Chemistry and Applications of Leuco Dyes

Edited by

Ramaiah Muthyala

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Foreword

Dye chemistry has seen a major resurgence of interest in recent years, as evidenced by increased conference activity and the publication of many new books in the field. This can be attributed to a virtual explosion of interest in dyes for speciality and high-technology applications (the *functional dyes*), and it is in these areas that the most exciting developments in dye chemistry and dye applications are occurring. For example, one of the consequences of the new information technology age is an unprecedented demand for “hard copy,” be it written text (e.g., laser-, ink-jet, or thermally printed), or photographic images (analogue or digitally generated). All of these processes use dyes and pigments in one form or another, colorants which command a very high unit price, and which often have very sophisticated structures. In this general area of imaging and copying, leuco dyes have a major part to play, and this brings us to the subject matter of this book.

The term leuco, meaning white, comes from the Greek, and was originally applied to the reduced form of vat dyes, e.g. indigoids or quinones, which were often (but by no means always) colorless. The alkali soluble *leuco*-vat dyes were, of course, extremely important in textile dyeing, as they provided the only means by which the highly insoluble parent vat dyes could be applied permanently to the fabric. The applications of *leuco*-dyes are now far more diverse than this, and the term is now applied to describe the (reversibly) reduced form of any class of dye. The term is also sometimes applied to the colorless form of a dye which may be produced by a nonreductive process, as for example, in the case of intramolecular cyclization, reactions induced by pH change, heat, or light. The important feature of all these reactions is color change, and it is principally this phenomenon that is exploited in so many new high-technology applications.

Given the diversity and the technical importance of *leuco*-dyes, it is surprising that until now no text book dedicated to this field has been published. The editor, Dr. Ramaiah Muthyala, a noted research chemist of long standing in the area of photoreprography, is to be commended for his perspicacity in appreciating this gap in the scientific literature, and for his skill in assembling a range of experts, including himself, to write chapters based on their own research experience, so producing a comprehensive and balanced book that will certainly be a classical text in the literature of dye chemistry.

The first chapter of the book deals with *leuco*-spiropyrans and related spiro compounds, which constitute one of the classes of *leuco* compounds not of the redox type. Such materials are photochromic, and are of major technical importance. The author, Hiroyuki Nakazumi of the Department of Applied Chemistry at the University of Osaka Prefecture, is well known for his researches in functional dye chemistry, particularly photochromic materials, and he provides a very useful update of the field, covering mechanisms, synthesis, spectra and applications, together with a useful section on approaches to near-infrared absorbing photochromic dyes.

Another noted and prolific Japanese author in the field of functional dyes, Masaru Matsuoka of the Laboratory of Materials Science, Kyoto Women's University, has written the second chapter, dealing with *leuco*-quinone dyes. These are the traditional redox *leuco* systems employed for so many years in the vat dyeing industry, and this chapter is an invaluable review of the chemistry of these systems, drawing on recent mechanistic and structural investigations. Applications considered include not only textile dyeing, but also other more specialized areas, such as hair dyeing, color formers, and photoimaging materials.

The third chapter deals with *leuco* derivatives of the oxazine, thiazine, and phenazine dyes, and is written by Tran Van Thien, who has had many years experience in photoimaging at the 3M Research Center, Harlow. His industrial experience in *leuco* dyes has enabled him to produce a collation of material impossible to find elsewhere in a single review, and again recipes for the synthesis of representative examples abound. Consideration is also given to the numerous applications of these molecules in thermal and photo-imaging systems.

Chapter 4 is concerned with a technically important group of *leuco* compounds which like the spiropyrans are not formed by reduction of the parent dye, but by formation of a spiro structure from the dye in such a way that the newly created sp^3 center destroys the conjugation, and hence, the color of the chromophore. These are the phthalides (spirolactones) and the position of equilibrium is determined by pH rather than a redox process. Such materials are used mainly as color formers in pressure-sensitive

copying paper, and in thermal recording paper. The two industrial authors, Ian J. Fletcher and Rudolf Zink, have long and distinguished careers in this field with the Chemicals Division of Ciba-Geigy, Grenzach, Germany, and they bring to bear on this chapter their intimate knowledge and wide experience of these materials.

The chemistry of these phthalides has much in common with that of the compounds reviewed in the next chapter, i.e., the *leuco*-triarylmethanes, and in fact, the parent dyes of the two classes share the same basic chromophoric system. However, the latter are true redox systems, rather than pH indicators, and consequently have a different range of technical applications. The situation is complicated further in that the triarylmethane cationic dyes can also bleach at high pH, giving a hydroxide addition product which is better described as a "carbinol base" rather than a "*leuco*" dye. Other nucleophiles (e.g., amines and cyanide ion) can add similarly to give colorless products. The authors have succeeded in covering all these complications thoroughly and logically, again giving due attention to technical applications and synthetic procedures. The editor has co-authored this chapter with Xiangfu Lan, who has had considerable academic and industrial experience in the field of heterocyclic chemistry and dye synthesis, and is currently a Senior Research Chemist with Clariant Corporation, United States.

Chapter 6 is rather more specialized than the others, in that it deals with a structurally narrow group of compounds, namely the *leuco*-fluorans. These are spiro-lactones and are dibenzofluoran analogues of the phthalides reviewed in Chapter 4. It might be argued that these compounds could have been subsumed into Chapter 4, but in practice the major technical importance of these materials in pressure-sensitive and thermal recording paper, and the very extensive patent literature that has built up around them, fully justifies their having a chapter to themselves. Yoshihiro Hatano is one of the world's leading experts in fluoran chemistry, and having had more than thirty years experience in this field with Yamamoto Chemicals Inc., Osaka, there could be no one more appropriate to author this chapter.

The final chapter deals with a unique class of *leuco*-compounds which turn the original concept of redox *leuco* dyes on its head. Tetrazolium salts are (largely) colorless and can justifiably be called *leuco* compounds, and yet on reduction they give intensely colored formazan dyes. Whereas most of the color-change systems dealt with in earlier chapters find greatest technical use in reprography, tetrazolium salts are more important in biochemical analysis. Nevertheless, it is clear from this chapter that the applications of tetrazolium salts are probably more diverse than those of any other class of *leuco*-compounds. It is fitting that the author, Daniel S. Daniel, is an expert in the biochemical applications of *leuco*-dyes, having had more than twenty

years relevant industrial experience, first with the Biosciences Research Division of Eastman Kodak Co., and currently with Johnson & Johnson Clinical Diagnostics.

The overall coverage of the book is most comprehensive, and as each chapter has been written by one or more recognized experts in the relevant field, one can be sure that the material covered is as topical and technologically relevant as it could be. Given that dye syntheses tend to be regarded by many chemists as either shrouded in mystery or buried inaccessibly in the patent literature, this book will be an essential laboratory reference text for the practical dye chemist, and an undoubted source of inspiration for those involved in the development of new high-technology materials.

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Preface

The field of dye chemistry has stimulated the publication of many books, monographs, special topics, and reviews over the years, but surprisingly, very little is mentioned about leuco dye chemistry- Color formers have been known for a long time. Many natural products are color formers and have become part of modern synthetic dyes, e.g., indigo, juglone, haematoxylin. The extensive utilization of indigo depended on the reduction of its color to a colorless water-soluble leuco form to facilitate dyeing and then regeneration of the color by oxidation on the fiber. Over the years, during the development of the synthetic dye industry, leuco materials played two major roles. First, many synthetic schemes make use of leuco materials as isolated intermediates in the final dye formation. Second, leuco dyes have a vital function in dyeing techniques. The entire vat dyeing industry hinged on the increased solubility of vat dyes when reduced and on the decreased solubility when reoxidized. Leuco forms of vat dyes were stabilized (trapped) and isolated as sulfuric acid esters and were marketed, for example, as indigo sols. Leuco dyes now play an ever-increasing role in modern applications, e.g., imaging, display, and memory technologies; and in analytical and biological sciences.

The use of the term *leuco dye* is a common paradox. Leuco color formers are materials that undergo controlled chemical or physical changes resulting in a shift from a colorless state to an intense color. The preparation of leuco color formers takes advantage of the very nature of colored materials themselves. The existence of extended conjugated π -system in dyes is responsible for the absorption in the visible region. The chemistry of such π -system is noted for facile reactivity, particularly to reactions such as reduction, oxidation, and hydrolysis (not hydrolytic cleavage). When π -

interaction is temporarily interrupted, the transition between the colored and colorless states is affected. The interrupted π -system is stabilized by a variety of trapping agents. The lifetime of a leuco dye (untrapped) can be milliseconds to several days or months, depending on the type of leuco dye. The use of unstable leuco dyes is restricted in modern applications such as imaging, although they can be of immense use in analytical and biological applications.

More recently, emphasis is shifting from natural dyes to synthetic dyes, to functional dyes. However, traditional organic synthesis has not caught up with the advances connected with functional dye chemistry. Hi-tech applications present many challenges to the dye chemist to devise dyes to meet the often demanding criteria. The leuco dye chemist, in addition to meeting all of the criteria associated with dyes, should maintain an optimum balance between reactivity and stability of the colorless form. This is not often obvious and is very challenging in its own right.

The growth of the leuco dye industry has created vigorous research activity in recent years, prompted by the great potential for proprietary products of high profitability. Because of the absence of ready sources, and the increasing importance of leuco dyes in modern applications, this book should prove to be both timely and useful. The present volume is designed to fulfill the needs of the novice researcher, and provide the general reader with an account of some selected areas of leuco dyes—mostly synthetic details and a few selected applications of important classes. This format, I believe, will be invaluable to both industry and academics alike. The book provides some experimental details, and directs the reader to the pertinent literature references. It is possible to prepare leuco compounds from a variety of dyes, for example, indoaniline, azomethine, and aminostyryl dyes. The majority of these leuco dyes are relatively unstable and their uses are restricted. Therefore, in this volume, only those leuco dye classes that have at least reasonable stability have been selected. Because of the tremendous amount of literature on leuco dye applications, complete description of applications of leuco dyes could not be justified; instead a major part is allocated to the chemistry.

The book is divided into seven chapters. Chapter 1 describes photochromic materials which have critical applications in memory technology. These compounds generally are activated by light. Chapter 2 covers leuco quinones which, in many cases, when oxidized, have their absorption maxima in the near-infrared region. Chapter 3 describes leuco dyes of a common group of compounds—oxazine, thiazine, and phenazines—that have found applications in color photography. Chapters 4–6 describe arylmethine-type compounds that can be triggered to dyes by common chemistry. Chapter 7 describes a special class of leuco dyes, namely, tetra-

zolium salts, which, unlike other dyes described in earlier chapters, become dyes by reduction, not by oxidation. The amount of literature available on this class is enormous, and page limitations have restricted its full description.

Readers interested in the role played by leuco dyes in hi-tech applications will find this volume to be useful and a reference for the future development of new classes of dyes or leuco dyes.

ACKNOWLEDGMENTS. It is a pleasure to gratefully acknowledge the contributors of this volume; without their hard work and kind cooperation this book would not have been possible. It is gratifying to acknowledge Drs. J. Kitchin and M. Matsuoka for their immense interest through the book's inception to its completion. I am especially grateful to Drs. A. R. Katritzky and G. Sabongi for asking me to take the responsibility for this volume, and for their constant support and advice. I sincerely thank Plenum Press for their cooperation. I am indebted to 3M management, particularly Barb Cederberg, Doug Dybvig, and G. Wagner who saw the benefit of this work to the company and to the scientific community. Finally I am thankful to my co-workers Doreen Lynch, Robert Balchunis, Rick Ollman, and William Ramsden for their support.

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1

Spiropyran Leuco Dyes

HIROYUKI NAKAZUMI

1.1. INTRODUCTION

The spiropyran is a pyran derivative linked by a common spiro carbon atom with another heterocyclic ring. Generally, the spiropyran absorbs in the UV region, but not in the visible region. On irradiation with UV light the spiropyran undergoes heterolytic cleavage of the carbon–oxygen bond to form the colored isomer, which is referred to as the “colored form,” “merocyanine form,” or “photomerocyanine form.” The conjugation between two heterocyclic rings is made possible by this cleavage. The resulting π -extended conjugation system in photomerocyanine causes absorption in the visible region (Scheme 1). The spiropyran compounds can be regarded as the leuco form of the merocyanine dyes.

In the merocyanine form, the electronic distribution should be described by delocalization of the π -electrons with a negative charge on the oxygen and with a positive charge on the heterocyclic ring. The two important forms—(A) dipolar zwitterionic form with localized charges and (B) quinoid form, a neutral species—are regarded as the basic skeleton of merocyanine dyes. However, a better structure would be represented by a hybrid of (A) and (B) with partial charges δ^+ and δ^- , as shown in Figure 1.1.

The stereochemistry of two central double bonds in the colored form of nonsymmetrical heterocyclic systems can be represented by four *cisoid*

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Chemistry and Applications of Leuco Dyes, edited by Muthyala. Plenum Press, New York, 1997.

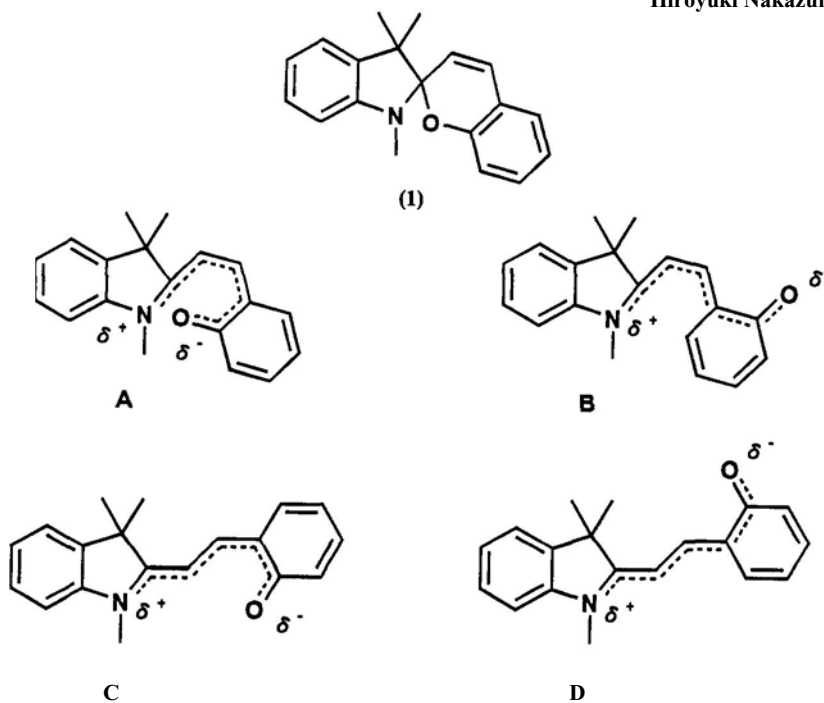
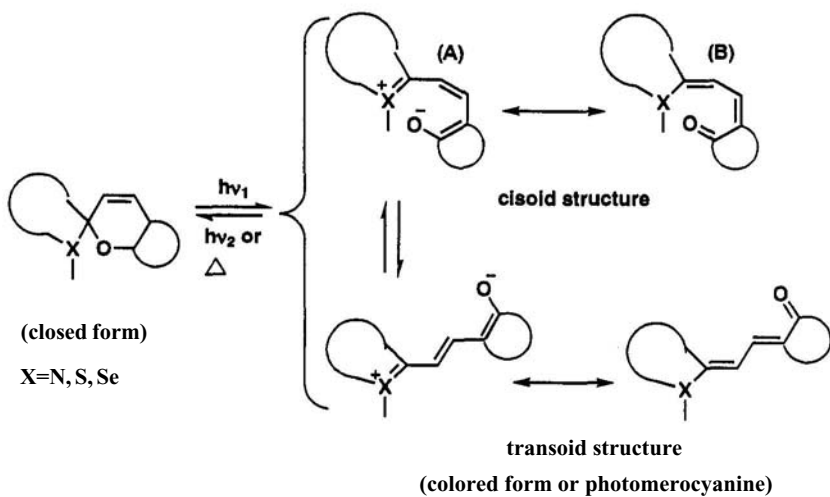


Figure1.1. Basic skeleton of the colored form in spiroindolinobenzopyran 1.



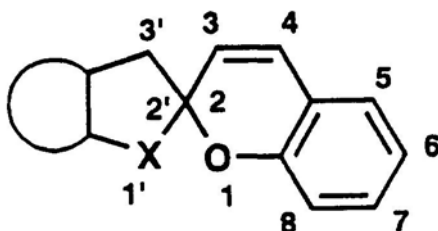


Figure 1.2. Numbering of spiropyran.

stereoisomers and four *transoid* stereoisomers. Typical *cis-cis*, *cis-trans*, *trans-cis*, and *trans-trans* isomers are illustrated in Figure 1.1.

The photochromism of the spiropyran depends on the structure of heterocyclic parts, the medium such as solvent or plastic films, temperature, and light energy. Though the actual mechanisms may be more complex, a simple photochromic behavior in the spiropyrans is illustrated in Scheme 1. Initially, a spiropyran is excited by photoirradiation, and then a *cisoid* isomer arises after dissociation of the C—O bond. Finally, the *cisoid* form changes to the thermodynamically stable *transoid* form. The equilibrium between the *cisoid* and *transoid* forms largely depends on the substituent groups. The reversal of the colored form to the colorless spiropyran occurs by thermal or photochemical energy. More detailed mechanisms will be described in Section 1.2.1.6.

The numbering of spiropyrans adopted throughout this review is indicated in Figure 1.2. The nomenclature of the spiropyran 1 is given as 1',3',3'-trimethyl-spiro[2H-1-benzopyran-2,2'-indoline]; it is referred to as spiroindolinobenzopyran and abbreviated as BIPS.

Over the years, many spiropyran structures have been prepared. The pyran component consists of benzopyran or naphthopyran and the heterocyclic part consists of indoline, benzothiazoline, benzoxazoline, benzoselenazoline, phenanthridine, acridine, quinoline, benzopyran, naphthopyran, xanthene, benzodithiole, benzoxathiole, and saturated heterocyclic rings such as pyrrolidine and thiazolidine.

Comprehensive and important reviews on photochromism of spiropyrans have been published by Bertelson¹ and Guglielmetti² In the present chapter, general synthetic methods and physical properties of spiropyrans with special reference to leuco dyes will be described. The chapter is divided into the spirobenzopyran, spironaphthooxazine, and spirothiopyran and related compounds.

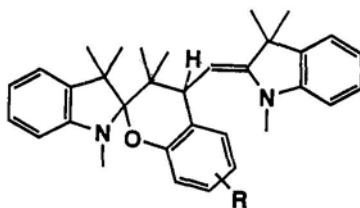
1.2. SPIROBENZOPYRAN

1.2.1. Spiroindolinobenzopyran (BIPS) and Related Series

1.2.1.1. Synthesis

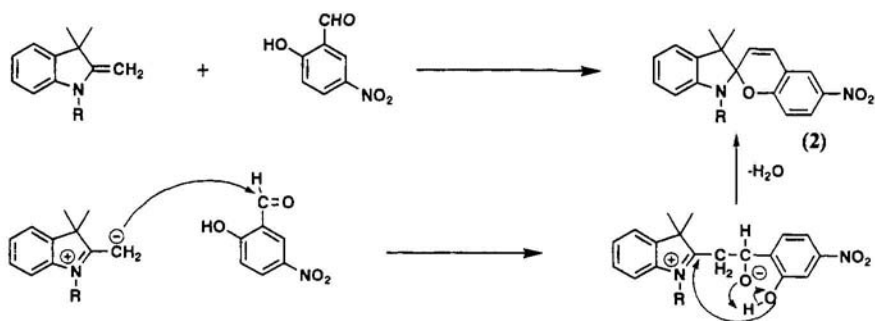
The spiroindolinobenzopyran **2** is a classical example of spiropyran and is easily prepared by the condensation of 1,3,3-trimethyl-2-methyleneindoline (Fischer's base) and salicylaldehyde in anhydrous ethanol or benzene (Scheme 2).^{1,2} The nucleophilic attack of Fischer's base on the carbonyl group (like an enamine) gives an aldol product, which undergoes ring closure followed by dehydration. This condensation is reversible; therefore, an exchange of the salicylaldehyde component of spiropyran with a different salicylaldehyde is possible. For example, when a solution of spiropyran **2** (Scheme 2) was refluxed with 3,5-dinitro-substituted salicylaldehyde, the open form of 6,8-dinitro-BIPS was obtained.²

The condensation of Fischer's base and salicylaldehyde does not always give spiropyran. Depending on the substituent group on salicylaldehydes, merocyanine dyes or tricyclic compounds are obtained. When a powerful electron-withdrawing substituted group, e.g., nitro group, is present in salicylaldehyde, condensation gives merocyanine dyes in benzothiazoline series,² and an electron-donating group leads to a condensed product **3** containing three heterocycles.¹

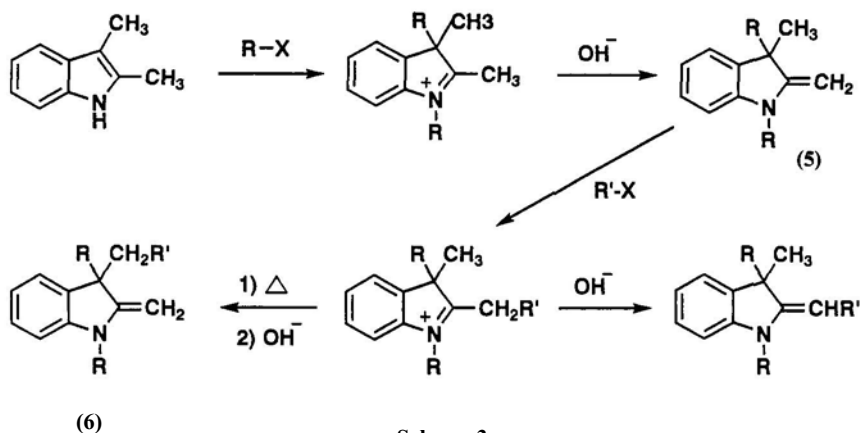
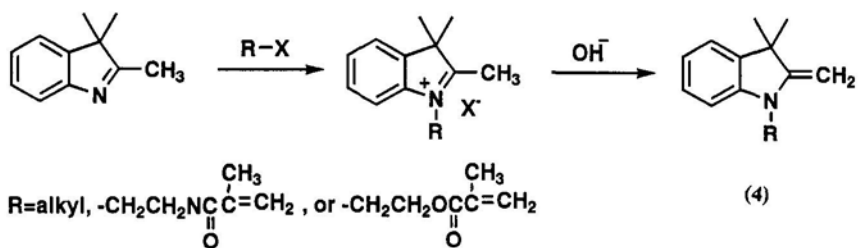


(3)

Fischer's base, a typical starting material, is commercially available and is also obtained *in situ* from the corresponding quaternary salt. *N*-substituted indolines **4** can be prepared by *N*-alkylation of 2,3,3-trimethyl-3*H*-indole followed by alkali treatment, or by exhaustive alkylation of 2,3-dimethylindole (*N*- and *C*-alkylation) followed by alkali treatment (Scheme 3). Further, methylation of indoline **5** with methyl iodide leads to *C*-methylation on the methylene group or the Plancher rearrange-



ment to give 3-ethyl-substituted indoline **6**.³ Reactivity of indoline **5** with higher alkyl iodide is very poor.³ However, *N*-(β -methylacryloylaminoethyl)- and *N*-(β -methacryloyloxyethyl)-spiroindolinobenzopyrans are made available for copolymers with polystyrene or poly(methylmethacrylate).⁴ Polyesters containing a spiroindolinobenzopyran are also pre-



Scheme 3

pared by condensation of bis(hydroxymethyl)spiroindolinobenzopyran with bisacid dichlorides followed by polyesterification with bisphenol A.⁵

Experimental Preparation of 6-nitrospiropyran 2 (R = Bu). Triethylamine (2.65 g, 26 mmol) was added to a suspension of 2,3,3-trimethyl-*N*-butylindolinium iodide (9.0 g, 26 mmol) and 5-nitro-salicylaldehyde (4.38 g, 26 mmol) in EtOH (100 ml) under stirring. The mixture was refluxed for 2 h, and filtered off. Recrystallization from hexane gave 6-nitrospiropyran **2** (R = Bu). Also, spiropyran **2** was isolated from the filtrate, which was evaporated under reduced pressure and then was chromatographed on silica gel with dichloromethane–methanol (60:1 v/v). Total yield of **2** (8.3 g) is 88%.

1.2.1.2. Molecular Structure

The X-ray crystal structures of some spiroindolinobenzopyrans, e.g., 8-NO₂-BIPS and 6-NO₂-8-Br-BIPS, have been determined by Russian researchers.^{6,7} Recently, X-ray crystal structures of the colorless form (**7a**) and the colored form (**7b**) of 6,8-dinitro-BIPS have been reported by Nakatsu⁸ (Figure 1.3).

In the colorless form (**7a**), the C2—O1 bond length (1.50 Å) is significantly longer than 1.43 Å found for the normal C—O bond length in benzopyran. The dihedral angle between an O1—C2—C33 plane and an N1'—C2'—C3' plane in two heterocyclic rings is ca. 90°, and heterocyclic rings are almost perpendicular to each other; nevertheless, they are not planar. The distance (2.68 Å) between the oxygen atom in the benzopyran and the carbon atom of methyl group at the 3'-position in the indoline ring is significantly shorter than the van der Waals radius for such atoms. This steric effect may aid in the ring opening. This C2—O1 bond extension and steric effect are similarly observed in spirothiazolinobenzopyran.⁹ From these observations, it is suggested that the C2—O1 bond is very weak and may easily be cleaved.

In the colored form (**7b**), the N1'—C2 bond length in the indolinium component is shorter than for the colorless form, indicating the double bond character. The C9—C10 bond length becomes longer than other C—C bonds in the phenolate ring. Alternation of the C—C bond length from C2 to C10 is reduced in the colored form. The strong interaction between phenolate oxygen with C3 or oxygen atom in the nitro group in the colored form is suggested, because of their shorter distances (Figure 1.3). In the solid state, the C9—O1 bond can be regarded as a carbonyl group. Thus, the molecular geometry in the colored form for **7** consists of an indolinium cation and negative phenolate ring. Therefore, suggestion of the polar

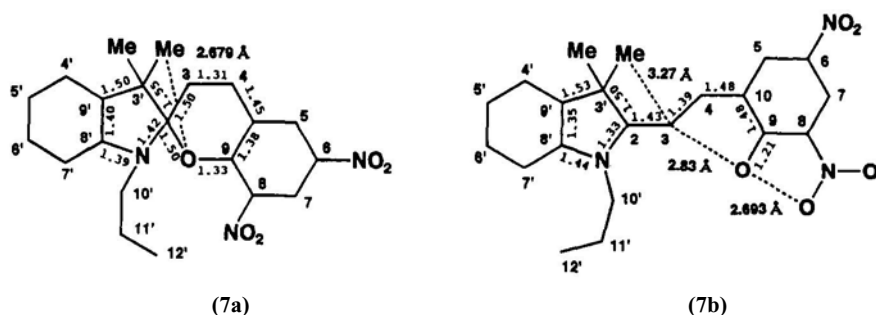


Figure 1.3. Structures of colorless form **7a** and colored form **7b** of spiropindolinobenzopyran **7** determined by X-ray analysis (estimated standard deviation 0.01–0.03).

zwitterion form is reasonable. However, the C—C bond in the conjugated chain is not always homogeneous in the merocyanine form for other spiropindolinobenzopyran series. For example, the C3—C4 bond is remarkably short (1.30–1.35 Å) in the photomerocyanine form of spiropindolinobenzopyran¹⁰ and spiropindolinnoxazolidine.⁸

1.2.1.3 Absorption Spectra of the Colored Form

Generally, measurement of absorption spectra of the colored form of spiropindolinobenzopyran is very difficult using normal spectrophotometry, as the colored form is thermally unstable. The absorption spectra of the colored form of 6,8-dinitro-BIPS **7**, which is exceptionally stable in DMSO even at 23°C, are shown in Figure 1.4. Generally, it is possible to obtain a reasonable absorption spectrum of the colored form by the use of a rapid scanning spectrophotometer.

The ring closed form (colorless form) has an absorption band below 400 nm, and the opened form has intense absorption in the visible region (above 350nm). The colored form of a spiropindolinobenzopyran has characteristic properties of a merocyanine dye. The shape and position of the visible absorption bands change significantly with solvent polarity. The visible absorption maximum generally shifts to a shorter wavelength together with decrease of the extinction coefficient and broadening of the band, as the polarity of the solvent increases.² This implies that the ground state of the colored form is relatively polar, and the polar solvents will stabilize the ground state of the colored form more so than the excited state. Concentration dependence of the colored forms in nonpolar solvents has been observed. At higher concentration, additional absorption bands and a

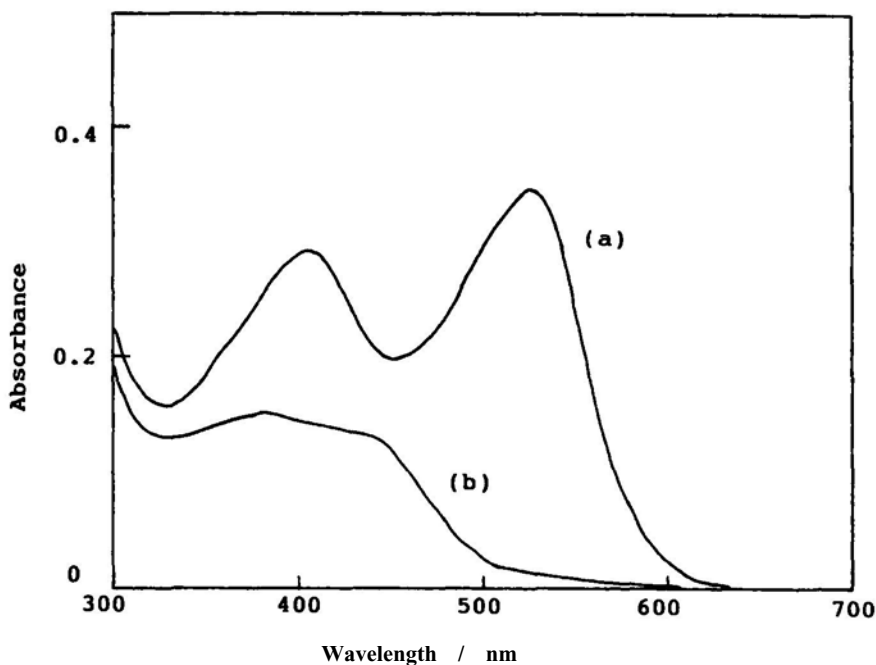


Figure 1.4. Absorption spectra of (a) the colored form (**7b**) of 6,8-dinitro-BIPS (2×10^{-5} M) and (b) the closed form (**7a**) produced by irradiation of (**7b**) with visible light in DMSO at 23°C.

shoulder appear on the shorter wavelength side. This has been assigned to a dimeric species or higher aggregation species. For example, absorption band at 490 nm of the colored form of 6-nitro-BIPS in benzene increases at higher concentration ($> 10^{-1}$ M)¹¹, whereas absorption bands at 596 and 555 nm increases at low concentration. However, in a polar solvent, such as ethanol, no additional peaks have been observed.

Absorption maxima for a wide range of heterocyclic systems are shown in Figure 1.5.² When the indolyl residue **8a** is replaced by other heterocyclic residue, a somewhat small shift in the λ_{max} occurs. Replacement with a benzothiazoline residue, **8c**, results in a bathochromic shift. Comparison between saturated heterocycles **8d–8f** and the corresponding benzoderivatives **8a–8c** shows that the conjugation produced by the benzene nuclei causes a bathochromic shift (ca. 20–50 nm). Replacement of saturated five-membered heterocycles by saturated six-membered heterocycles results in a hypsochromic shift. In the case of the piperidine series (**8g**) a significant hypsochromic shift occurs, due to steric hindrance in the colored form.

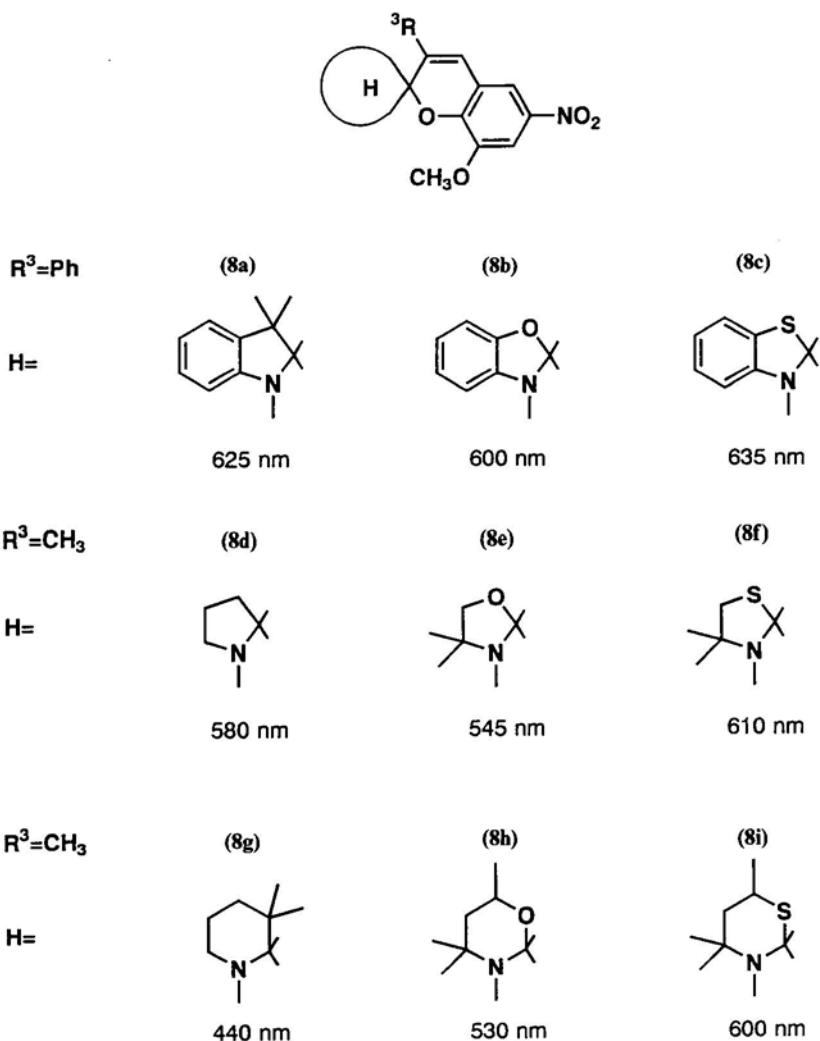
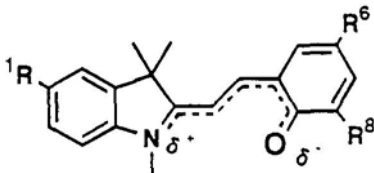


Figure 1.5. λ_{max} of the colored form for spirobenzopyrans containing various heterocyclic systems in toluene.

Remarkable substituent effects on the absorption bands in the colored form are observed on substitution in positions 3, 6, and 8 of the spirobenzopyran (Table 1). A nitro group at the 8-position yields a higher λ_{max} (~40nm) compared with a nitro group at the 6-position due to interaction of phenolate anion and oxygen atom of the nitro group. In many cases, it

Table 1. Absorption Maxima of the Colored Form of 6,8-Disubstituted Spiroindolinobenzopyrans in Ethanol¹

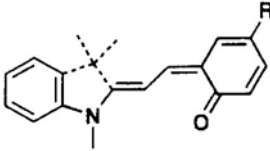
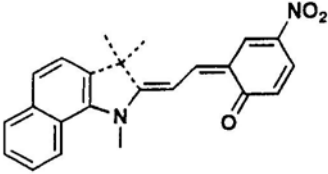
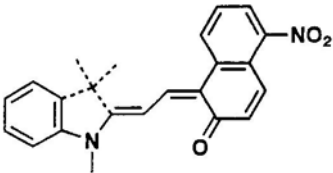
				
Compound	R ⁶	R ⁸	R ¹	λ _{max} , nm
(9a)	NO ₂	H	H	532
(9b)	H	NO ₂	H	544
(9c)	NO ₂	MeO	5'-Br	550
(9d)	MeO	NO ₂	5'-Br	590
(9e)	NO ₂	MeO	5'-Ph	568
(9f)	MeO	NO ₂	5'Ph	625
(9g)	NO ₂	Br	H	533
(9h)	Br	NO ₂	H	570
(9i)	NO ₂	C1	H	535
(9j)	C1	NO ₂	H	560

has been shown that the steric hindrance of the substituent in 3-position causes a bathochromic shift of λ_{max}.² Replacement by an electron-withdrawing group, such as a nitro group, on the heterocyclic cation residue causes a bathochromic shift. The available data on other colored forms are collected in Ref. 1.

The absorption bands for both quinoid and dipolar structures have been calculated by the PPP method.^{2,12} The calculations for a more simplified model of the colored form of some spirobenzopyrans using the normal parameters are shown in Table 2.¹² In this case, the spiro carbon in the indoline moiety is ignored in the π-electron system, and the quinoid structure is assumed.

PPP calculations reproduce the nitro substituent effect and heterocyclic effect on the λ_{max}. For example, the bathochromic shift by substitution of a nitro group is calculated (ca.20nm). It is in good agreement with the experimental value determined (λ_{max} = 598 nm) in toluene. PPP calculation exactly predicts the bathochromic shift by benzo-annulation of the indoline and benzopyran residues (Table 2). In the neutral quinoid form, the calculated charge densities for the ground and first excited states by PPP

Table 2. PPP Calculation of the Colored Form of Spiroindolinobenzopyrans

Compound	R	Expt ^a $\lambda_{\max}, \text{nm}$	Calcd. ^c $\lambda_{\max}, \text{nm}(f)^d$
	H NO ₂	576 ^b 598	581(1.37) 604(1.34)
		620	625(1.52)
		572	577(1.39)

^aIn toluene.^bIn 1,4-dioxane.^c E_i (ionization potential) = 13.6 eV, γ_n = 6.08 eV for N atom of indoline ring is used in PPP calculation. The sp^3 carbon for indoline component is ignored for PPP calculation. Other parameters listed in Ref. 15.^dOscillator strength.

calculation are shown in Figure 1.6, indicating that the colored form is relatively more polar in the excited state than in the ground state.

The absorption band of the colored form of many spirobenzopyrans occurs in a narrow range (ca. 550–600 nm). An approach to vary the color of the spiropyran with some limits is possible if molecular design is performed using the stable colored form. For example, cationic dye **10** is very stable and its chromophore is the conjugated polymethine, as shown in Scheme 4 (dotted line). A carbonyl group at C4 leads to a ring closure to give spiropyran containing benzopyrylium or benzothiopyrylium residue. These have been designed with the PPP method, as described in Section 1.4.1. Introduction of a π -conjugated donor group into the 2-position of benzopyran (R^1) and/or replacement by a nitro-substituted group in the indoline residue (R^2) is expected to produce a bathochromic shift of $\lambda_{\max}$

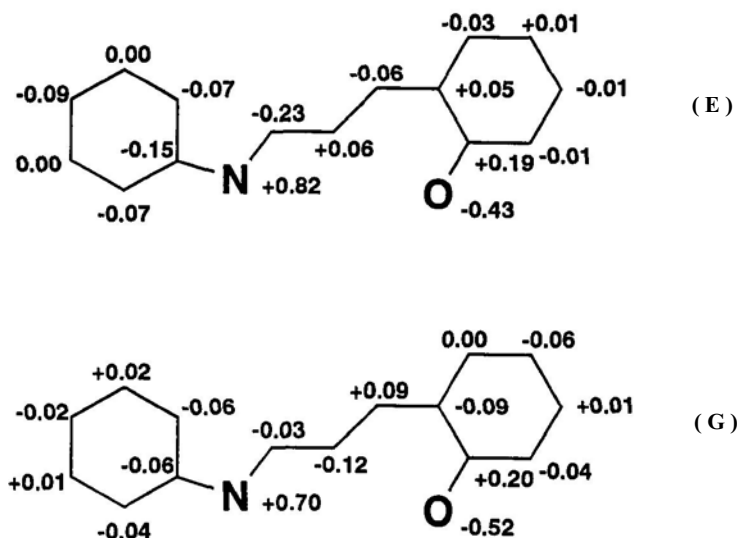


Figure 1.6. Net charge densities for π -electron system of the colored form of **1** in the ground (G) and the first excited (E) states.

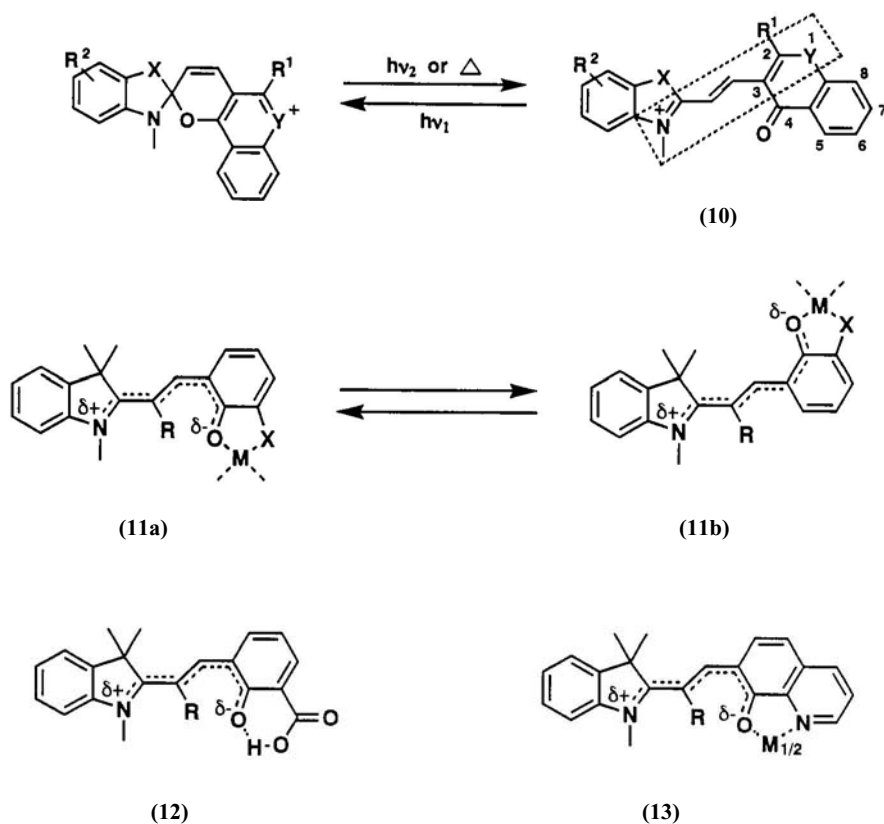
(Table 3).¹³ Experimentally, the extension of the π -conjugated chain resulted in a reasonably bathochromic shift, and consequently the color changes from yellow to green. But the ring-closure reaction rate significantly decreases on introduction of a conjugated donor group into the 2-position of the benzopyran ring.

Table 3. PPP Calculations of Benzopyrano- and Benzothiopyrano-merocyanine Dyes (**10**)

Substituents			$\lambda_{\max, \text{nm}}$	
X	Y	R ¹ , R ²	Expt. (log ϵ) ^a	Calcd. (f) ^b
C(CH ₃) ₂	O	H, H	403(4.48)	430(1.23)
C(CH ₃) ₂	S	H, H	456(4.54)	429(1.16)
S	S	H, H	435(4.58)	420(1.10)
C(CH ₃) ₂	O	—CH=CH—NMe ₂ , H	556(4.54)	534(1.27)
C(CH ₃) ₂	O	—CH=CH—(C ₆ H ₄ - <i>p</i> -NMe ₂), H	651 (4.53)	709 (1.15)
C(CH ₃) ₂	O	—CH=CH—(C ₆ H ₄ - <i>p</i> -NMe ₂)	725(4.57)	749 (1.23)
		NO ₂		

^aIn CHCl₂CHCl₂.

^bOscillator strength.

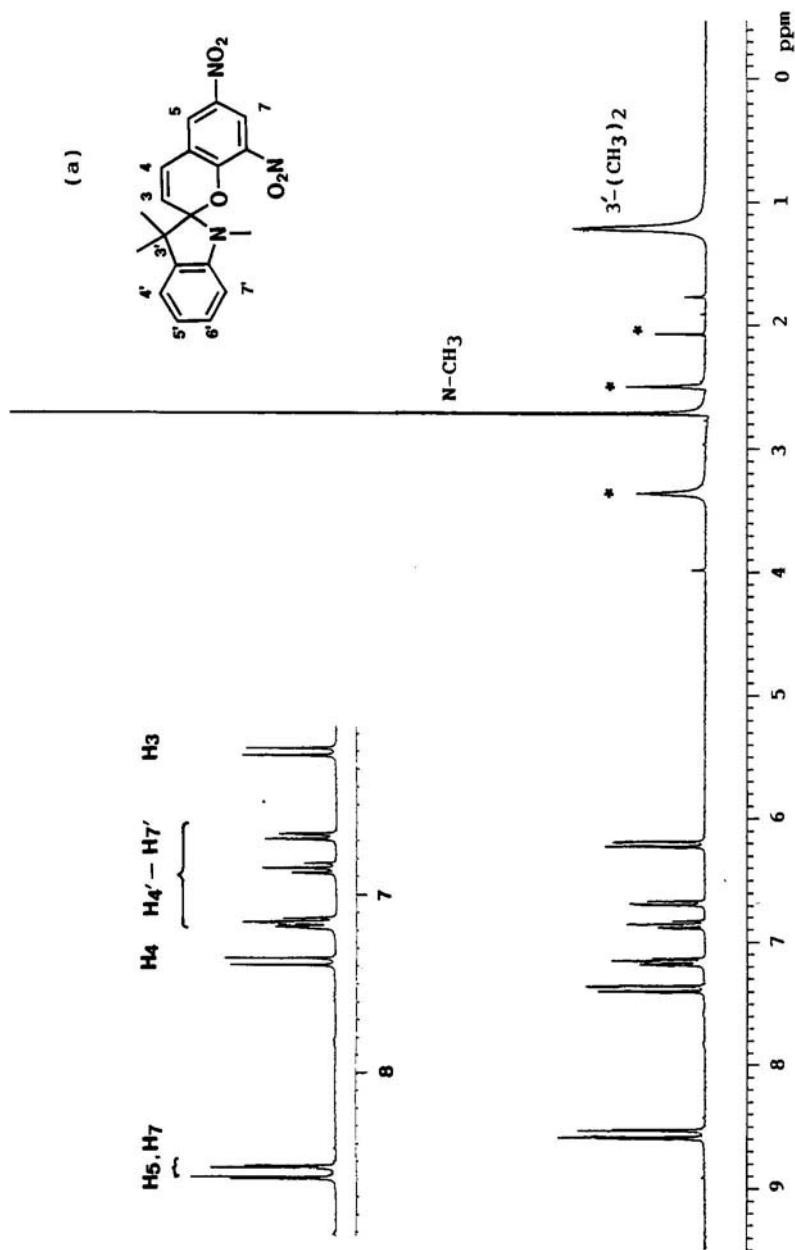


Scheme 4

1.2.1.4. $^1\text{H-NMR}$ Spectra

NMR spectroscopy is a convenient method for structural study of the equilibrium between the colored and the colorless form of spirobenzopyran. In the $^1\text{H-NMR}$ spectra, the chemical shifts of *gem* methyl groups in 3'-position, *N*-methyl group,^{2,11} and methine protons in 3- and 4-position are important to distinguish between the colored and colorless forms.

Typical $^1\text{H-NMR}$ spectra (e.g., 6,8-dinitro-BIPS 7) of the colored form and colorless form are shown in Figure 1.7. The resonance peak for 3'-methyl groups in the colored form shifted to low field by 0.5 δ , compared with that of the colorless form.² Generally, for *N*-methyl groups, the peak appears at ca. δ 2.7–3.0 and 4.0–4.30 in the colorless and the colored form, respectively.



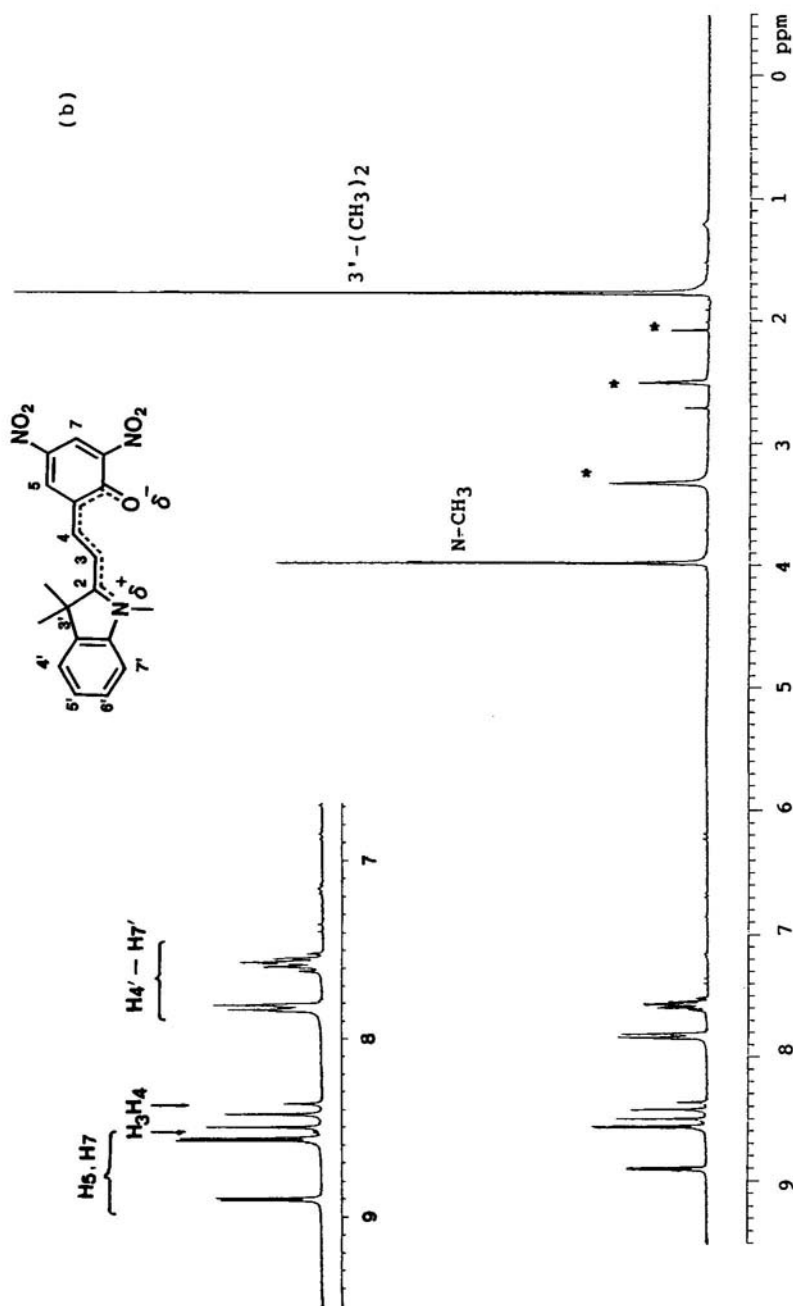


Figure 1.7. FT ¹H-NMR (270 MHz) spectra of (a) the colorless form and (b) the colored form of 6,8-dinitro-BIPS 7 in DMSO-*d*₆ (asterisks indicate solvent peaks).

The resonance peaks of two methine protons at 3,4-position are important for determining the geometry of 3,4-double bond. In the colorless form, the two methine protons appear at δ 6.0–6.4 (H_3) and 7.2–7.4 (H_4 , $J = 10$ Hz) which have been assigned to the *cis* configuration. In the colored form, they shift to low field to δ 8.4–8.6 and 8.2–8.4 ($J = 15$ Hz), respectively, and especially the peak of the 3-hydrogen appears at low field, due to a specific interaction with the phenolate oxygen atom.^{14,16} Thus, a favored configuration is *trans* configuration C (Figure 1.1) for the colored form and other *trans* configuration D is possible when the colored form has an alkoxy and aryloxy group in the 3-position. The ^{13}C chemical shifts and coupling constants for spirobenzopyrans with various heterocycles have been compiled.²

1.2.1.5. The Stabilization and Chelation of the Colored Forms

The thermal fading of the colored form follows first-order kinetics.¹ The substituent effects in the pyran component obey Hammett-type correlation.² For example, the value of ρ for the thermal fading rate of spiroindolinobenzopyrans having substitution only in the pyran portion is -1.8 to -3.45 . The electron-donating group in the indoline component stabilizes the colored form by decreasing the thermal fading rate which is also dependent on solvent, temperature, substituent groups, and heterocyclic components. The rate constant for thermal fading of the spiroindolinobenzopyran without a substituent group in the 3-position is generally 1.4×10^{-3} – $4.8 \times 10^{-2} \text{ s}^{-1}$ in toluene.¹

The substituent effect in the phenyl group at the 3-position is also observed in the benzothiazoline series.^{2,17} The thermal fading rate increases with the bulky group at the 3-position, but the colored forms of 3-methoxy and 3-phenoxy derivatives are largely stabilized by an intramolecular interaction with 5-hydrogen atom.²

The chelation of the colored form with metal ion is possible for spirobenzopyrans having a donor substituent group at the 8-position, acting as bidentate ligand groups. These groups can be $-\text{OCH}_3$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{OR}$, $-\text{CH}_2\text{NR}_2$, $-\text{CH}=\text{NR}$, or $-\text{N}=\text{N}-\text{Ar}$.¹⁸ The formation of the stable chelates of the colored form with divalent metals, e.g., Zn^{2+} , CO^{2+} , Ni^{2+} , and Cu^{2+} , has been qualitatively demonstrated. The structures of these complexes are not always established. In the spiroindolino- and spirobenzothiazolino-benzopyrans with such substituent groups, the C—O bond in the colorless form can be broken by metal salts to give complexes.⁷ Spiropyran possessing a bidentate ligand forms two bonds with a metal ion, giving metal complex, **11a** or **11b** which depends on the substituent group at the 3-position due to steric hindrance. Metals such as cobalt give a

mixture of monomeric and dimeric complexes. The geometry of the dimeric complex consists of polyhedral coordinations to the Co ion¹⁹; however, the heterocyclic plane and phenyl ring maintain a bent conformation (like a *cisoid* form) and the nonbonding C2—O1 distance (2.65 Å) in this metal complex is within the van der Waals radii.

Instead of metal chelation, an intramolecular hydrogen bonding between the oxygen atom of phenolate and a hydrogen atom of a carboxylic acid in the 8-position leads to stabilization of the colored form, such as compound **12**.^{20,21} This spiropyran exhibits reversed photochromism, which means that thermally stable species change from the spiro form to the colored form, and thus the colorless form produced by photoirradiation soon converts to thermally stable colored form.

In the presence of acid, unsubstituted BIPS assumes a thermally stable protonated colored form, and shows reversed photochromism, in which the phenolate form changes to a phenol.^{20,22} In this case, the absorption band remarkably shifts to the short wavelength. For example, in the presence of acid the absorption band of 6-nitro-BIPS occurs at 405 nm in acetone.

The spiropyran containing a quinoline ring forms a stable chelate **13** by reacting Cu²⁺ or Fe³⁺ ions with the colored form, produced by photoirradiation, or by irradiation of a solution of spiropyridopyran containing a metal ion.^{23,24} 7-Amino-spiropyridopyran also gives a colored complex with guanosine derivative by intermolecular hydrogen bonding.²⁵

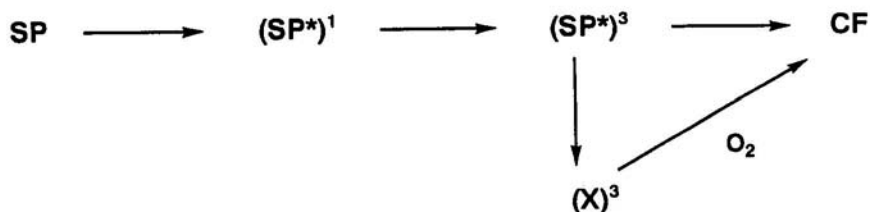
1.2.1.6. Mechanism of Coloration of Spiropyran Generated by Photophysical Process

The spiropyran gives the colored merocyanine form by photodissociation of the spiro C—O bond. Generally, the ring-open reaction of spiroindolinobenzopyrans proceeds via the following mechanism: The weakening of the C—O bond due to photochemical activation of the π -electron system of the spiropyran (SP*)¹ (Scheme 5), and the dissociation of C—O bond depends on the interaction of the electrons of the nitrogen-nonbonding orbital and the unoccupied antibonding orbital (σ^*) of the spiro C—O bond. The electron-donating substituent group in the spiroindolinobenzopyrans has a tendency to increase the polarization of the C—O bond.

In the case of spiroindolinobenzopyrans without a nitro group, the photocoloring reaction generally proceeds via the excited singlet state of the



Scheme 5



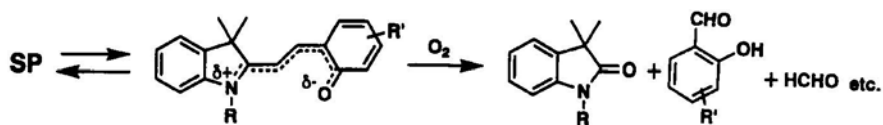
Scheme 6

molecule, and then formation of the *cis-cisoid* isomer X (A in Figure 1.1). Finally, a *cis-trans* isomerization gives a *transoid* colored form (CF) (Scheme 5). For spiropyrans having an extended aromatic π system such as spiroindolinonaphthopyrans the photocoloring reaction also proceeds via the singlet state. The *cis-cisoid* isomer X has been proposed to be an intermediate in the isomerization of spiropyrans containing a heterocyclic component such as indoline, oxazine, and thiazine.^{26,27} Such short-lived intermediate (lifetime 10^{-8} – 10^{-3} s; $\lambda_{\max}$ 430–450 nm) in photocoloring reaction has been detected by the pulse spectroscopic technique.^{28–30}

The photocoloring reaction for spiroindolinobenzopyrans with a nitro group proceeds mainly via the formation of the excited triplet state of the molecule. The reaction proceeds partly from the triplet state [(SP*)³] of the spiropyran to the triplet state (X)³ of the *cis-cisoid* isomer which subsequently transforms into the CF and partly from (SP*)³ to the CF. This process from (X)³ to the colored form is accelerated by the presence of atmospheric oxygen (Scheme 6).^{2,28} For the photocoloring reaction, the participation of singlet or triplet state depends not only on the substituent but also on the nature of the heterocyclic component.

The quantum yields for photocoloration of spirobenzopyrans are collected in Ref. 1. Generally, the coloration quantum yields of spiroindolinobenzopyrans by UV irradiation (366 nm) at room temperature (15–25°C) are 0.1–0.7. Photobleaching quantum yields by visible light are very small (<0.1) and less accurate, since both thermal and photobleaching occur simultaneously.

The nitro substituent has significant influence on photofading of spiroindolinobenzopyrans and the BIPS systems. Without a nitro group, they show better stability to the light. The electron-withdrawing substituent in spirobenzopyrans decreases the polarization of the C—O bond, leading to less likely homolytic cleavage of the C—O bond. This is largely responsible for the degradation of the spirobenzopyrans.^{1,31} The solvent also has a direct influence on the polarization of the C—O bond. The spirobenzopyrans show better stability to the UV light when the solvents have a high



Scheme 7

degree of solvation (polar solvent).² Photofading of spiroindolinobenzopyrans in aerated solution produced partially oxidized products, such as salicylaldehyde derivative, oxindole, formaldehyde, and oxidized derivatives of solvents (Scheme 7).³²⁻³⁴

1.2.1.7. Applications

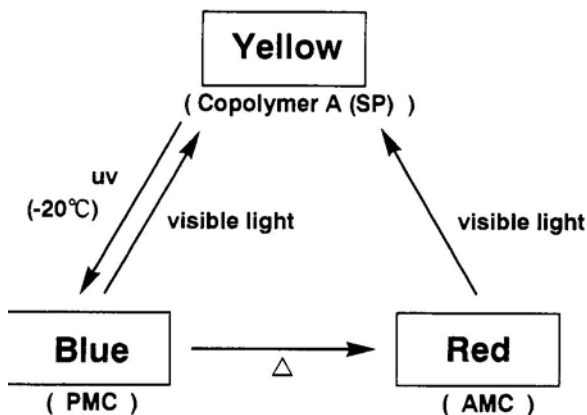
Applications of photochromic materials take advantage of a specific color change, and are found especially in the field of decorations, such as textiles and paints.^{1,2} The systems that utilize reverse coloration of photochromic compound are sunglasses, car windows, windowpane, information storage, and display media. Light sensitivity of photochromic materials is much lower than that of silver halides. However, they have sufficient sensitivity to laser light and UV light sources. Although spirobenzopyran is not useful for practical applications, spirooxazine and spirobenzothioipyran are practically useful for sunglasses and optical data storage, respectively.

Polymers containing photochromic compound, such as spiroindolinobenzopyran, have much more practical use than simple monomeric compounds. In the polymer matrix, the equilibrium between spiropyran and photomerocyanine forms depends on the temperature and polymer matrix, and the glass transition temperature.³⁵ However, when photochromic polymer, e.g., containing spirobenzopyran, is irradiated by UV light at high temperature, it may no longer exhibit color, since under these conditions, photocoloration and thermal fading reaction may be competitive.

The photochromisms of spiroindolinobenzopyrans trapped in glass prepared by the sol-gel method have been studied.^{36,37}

For thermographic recording materials, thermochromic properties of the spiroindolino- and spirobenzothiazolino-benzopyrans have been utilized. As an example, thermal paper patented by National Cash Register³⁸ can be cited. In this paper, the colored merocyanine form is fixed by reacting with phenols or metallic salts.²

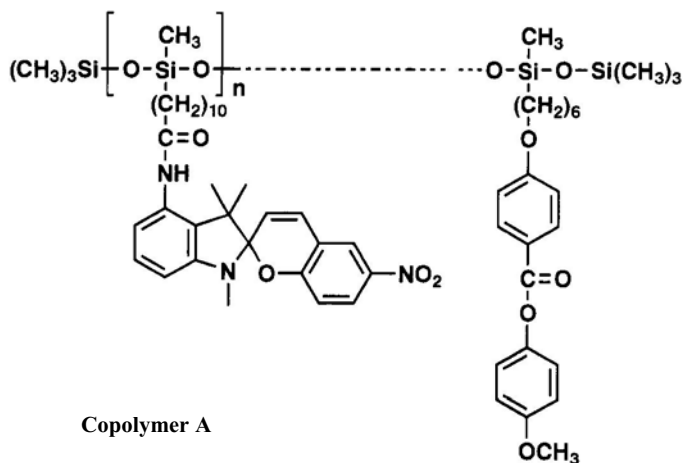
Solid films of spiropyran are important in optical data storage. Thin films of spirobenzopyran (1.0 μm) have been prepared by vacuum deposition, and its reversible photochromism has been confirmed.³⁹ The J-aggre-



SP : spiropyran form in copolymer A

PMC: photomerocyanine form in copolymer A

AMC: aggregate photomerocyanine form in copolymer A



Scheme 8

gation form of photomerocyanine in Langmuir–Blodgett (LB) film is attempted in multi-optical data storage using at least two laser.^{46,47}

Photochromic materials with liquid-crystal polymer^{40–42} are interesting advanced materials, due to their sensitivity to light, electric, and magnetic fields. Copolymers of polyacrylic or polysiloxane backbone, con-

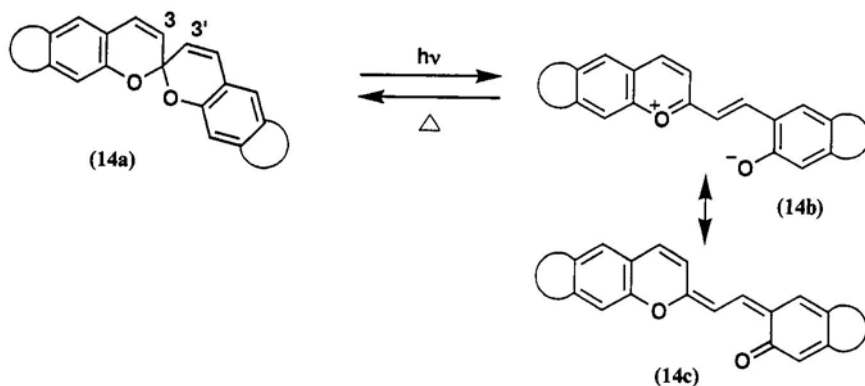
taining a high percentage of spirobenzopyran and a mesogenic group, have been prepared. In such compositions, aggregation of the colored form with stacklike structure is formed.^{43–45} For example, when the yellow film of polymer A is irradiated with UV light below -20°C , the blue colored form (580 nm), i.e., normal photomerocyanine form, is produced. Heating the blue film to 25°C produced red coloration (Scheme 8).⁴² This colored form is the H-aggregated polymer of photomerocyanine, in which the molecular dipole is antiparallel, absorbing at λ_{max} 550 nm. The yellow form can be reversed from the red or blue form with visible light. Thus, basic three color forms from copolymer A can be produced by reversible reaction, as shown in Scheme 8.

1.2.2. Spirobenzopyranobenzopyran

1.2.2.1. Introduction

A number of spirobenzopyranobenzopyrans, **14**, in which two benzopyran components are linked via 2-spiro carbon, were prepared in the 1960s and 1970s.^{1,48} These compounds are also called spirodibenzopyrans or dichromenes, and they exhibit photochromic properties (Scheme 9). Four geometrical isomers for colorless forms can theoretically exist for spirodibenzopyrans having different substituent groups at the 3,3'-positions. Isolation of these isomers has been attempted, but only one isomer has been isolated by general workup.^{1,49}

The photocolored form is assumed to form via the heterolytic cleavage of the C—O bond. Studies on the thermal fading kinetics have shown^{2,50}



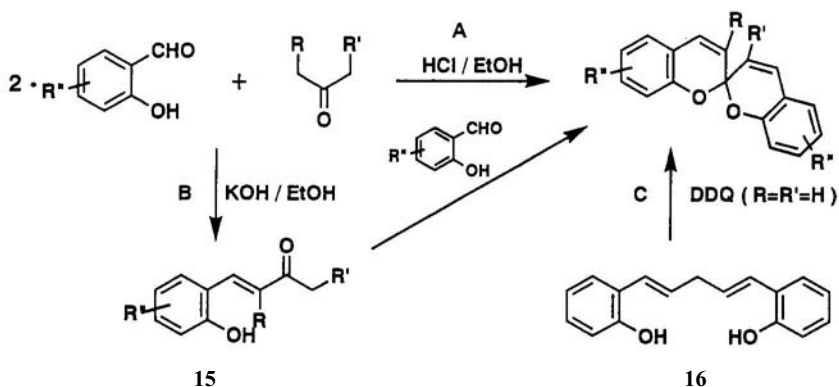
Scheme 9

that the closed form is thermally stable at room temperature. Comparison between spirodibenzopyran and spiroindolinobenzopyran shows that the thermal fading rate of the photocolored form is almost similar in both series. The steric hindrance of a substituent group on the 3- and/or 3'-position of spirodibenzopyran affects the thermal fading rate of the colored form. Thermal fading is also affected by the substituent groups and annelated benzopyran. The thermal fading rate constants for 3-substituted derivatives are in the range of 2.0 to $3.75 \times 10^2 \text{ s}^{-1}$ at 25°C in toluene.

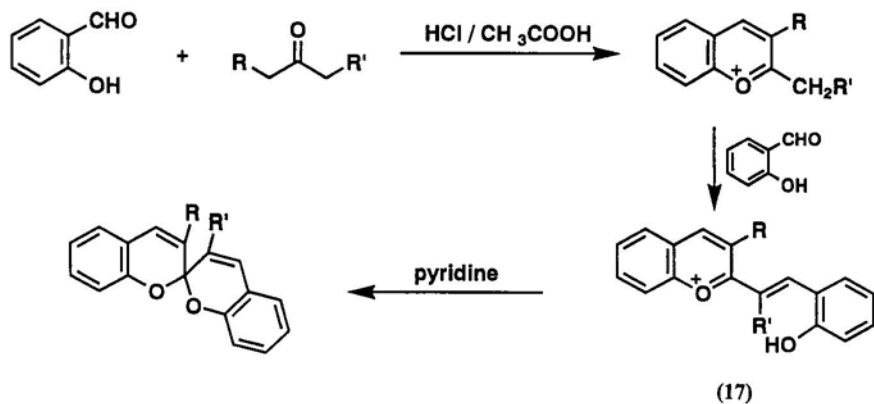
1.2.2.2. Synthesis and Absorption Spectra

Spirodibenzopyrans are prepared by two principal routes: (A) condensation of two equivalents of salicylaldehyde with appropriate ketone; (B) condensation of *o*-hydroxystyrylketone **15**, which is prepared from salicylaldehyde and a ketone in the presence of KOH, with the same or different salicylaldehyde derivatives, as shown in Scheme 10.^{2,48} Spirodibenzopyran can also be obtained from 1,5-bis(2-hydroxyphenyl)-1,4-pentadiene **16** by dehydrogenative reaction (C).⁴⁸

Method B involves the preparation of precursor of 2-alkyl-1-benzopyrylium salts, as shown in Scheme 11.⁵⁰ 2-Alkylbenzopyrylium salts have been prepared by condensation of salicylaldehyde with appropriate ketone in acetic acid or by alkylation or reduction of coumarin or chromone derivatives. Reaction of 2-alkylbenzopyrylium salts with salicylaldehyde gives directly a spirodibenzopyran or 2-vinynologue benzopyrylium salt **17** which then can be converted into the spirodibenzopyran by piperidine or pyridine.

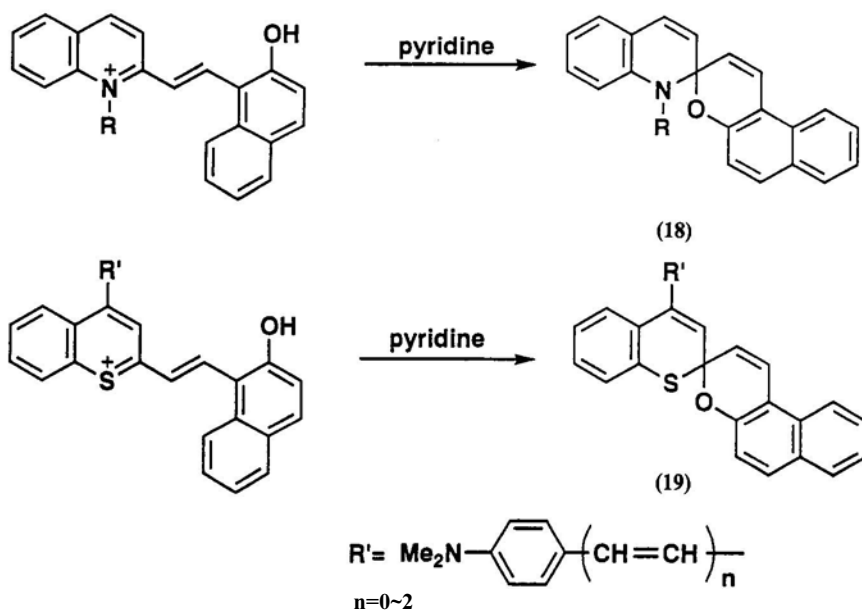


Scheme 10



Scheme 11

Heteroanalogues of spirodibenzopyran, such as spiroquinolinonaphthopyran **18** and spirobenzothiopyranonaphthopyran **19**, are similarly prepared from the corresponding quinolinium salts and benzothiopyrylium salts, respectively (Scheme 12)^{51,52} Spirobenzothiopyranonaphthopyran **19** has an extended π -conjugation in 4'-position, and its photomerocyanine



Scheme 12

Table 4. $\lambda_{\max}$ of the Photocolored Form of the Spirodibenzopyran Series in 1,4-Dioxane

	485 nm ^{53,54}		560 nm ^{1,54,55}								
(20)		(21)									
	561 nm ¹										
(22)		(23)									
		<table> <tr> <td>H</td> <td>590 nm^{1,55,56}</td> </tr> <tr> <td>6-Cl-3-Me</td> <td>489 nm¹</td> </tr> <tr> <td>6-Cl-3-Me-8'-NO₂</td> <td>551 nm¹</td> </tr> <tr> <td>7-N(CH₃)₂-3-Me-8'-NO₂</td> <td>627 nm¹</td> </tr> </table>	H	590 nm ^{1,55,56}	6-Cl-3-Me	489 nm ¹	6-Cl-3-Me-8'-NO ₂	551 nm ¹	7-N(CH ₃) ₂ -3-Me-8'-NO ₂	627 nm ¹	
H	590 nm ^{1,55,56}										
6-Cl-3-Me	489 nm ¹										
6-Cl-3-Me-8'-NO ₂	551 nm ¹										
7-N(CH ₃) ₂ -3-Me-8'-NO ₂	627 nm ¹										

form absorbs in the near infrared region (692–858nm). However, this photomerocyanine form is stable and is not reversed to the spiropyran form.⁵²

The colored form of spirodibenzopyran can also be regarded as merocyanine chromophore. For photomerocyanine structure, the contribution of the zwitterionic form (**14b**) may be greater than the quinoid form (**14c**), since the stability of the charge separation leads to favorable formation of the aromatic benzopyrylium ring and benzene ring. However, the $\lambda_{\max}$ of colored forms in some spirodibenzopyrans shifts to longer wavelength when polarity of the solvent is increased,¹ suggesting that the quinoid form is dominant in the photocolored form.

Annulation of the benzopyran in spirodibenzopyran series results in remarkably bathochromic shift of the absorption band in the colored form, as shown in Table 4. The $\lambda_{\max}$ of the colored form in **21–23** shifts to longer wavelength of about 80–100 nm, compared to the parent spirodibenzopyran **20**.

Substituent effects on the $\lambda_{\max}$ of the colored form in these series are interesting and are dependent on the pyran component. For compound **20**, substitutions at position 3, 6, or 8 (or 3', 6', 8') affects the $\lambda_{\max}$ substantially, i.e., the absorption band lies in a wide range 475–609nm. The 7,7', 8,8', or 10,10'-dinitro-substituted compounds **21** reveal a somewhat hypsochromic shift, relative to unsubstituted derivative, whereas the bathochromic shift (10–40 nm) is observed with dinitro substitution at the same position in compound **22**. For compound **23**, the pronounced shift is also observed with 8-nitro substitution. Many other spectral data are collected in Ref. 1.

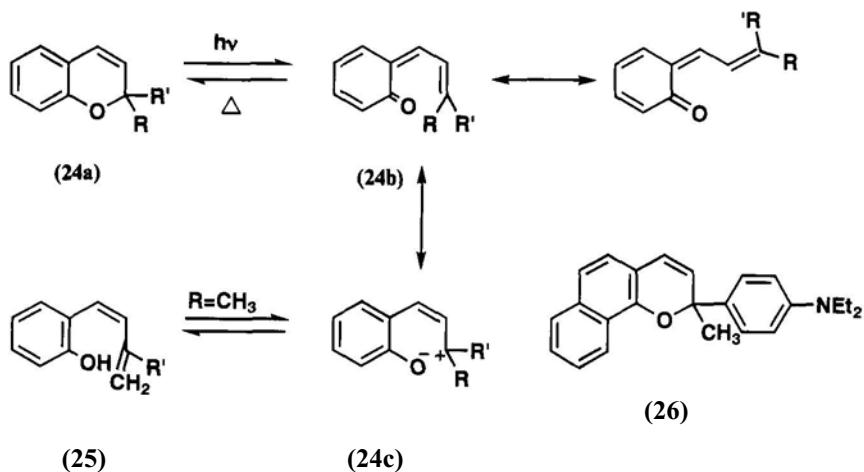
1.2.3. 2,2-Dialkylchromene

Many 2,2-dialkylchromenes, e.g., gambogic acid and flemingins, have been discovered in nature.⁴⁸ 2,2-Dialkylchromenes exhibit photochromic behavior, and their colored forms generally show yellow to orange hue.⁵⁷ The chromene structure is thermally stable at room temperature, and the colored form is produced by irradiation in approximately 50s in toluene at 24°C.⁵⁸ Studies on the mechanism of photocoloration of 2,2'-dialkylchromene indicate that the colored form for chromenes containing no nitro group occurs from the excited singlet state of the chromene⁵⁹ and for nitro-substituted chromenes, it occurs partly from the excited singlet state and partly from the triplet state of the *cisoid* form.

If R or R' is not an amino group, the *ortho*-quinoid structure **24b** is preferred over the zwitterionic structure **24c** for the colored form, since there is no additional conjugation to stabilize the carbonium ion produced by irradiation. Kolc and Becker first postulated the *ortho*-quinoid structure for the colored form which was produced at low temperature and trapped by reduction with LiAlH₄.⁶⁰ It is reported that the *cisoid* form produced by photoirradiation undergoes a 1,7-hydrogen shift to the phenol **25** when R is a methyl group (Scheme 13).⁶¹ When R (or R') is a donor group, such as an amino group, the zwitterionic form is stabilized, and the $\lambda_{\max}$ of the colored form is significantly redshifted. For example, the colored form of 6-nitro-8-methoxy-2,2,3-trimethylchromene has two bands at 370 and 500m.⁵⁸ In the case of 2-(*N*-carbazolyl)-6-nitro chromene (**24**, R' = H, R = *N*-carbazolyl), the $\lambda_{\max}$ is at 520 nm. The colored form of 2-methyl-2-(*p*-diethylaminophenyl)naphthopyran **26** also absorbs at 550 nm.⁶²

Merlini has presented a detailed review of preparation of some 2,2-dialkylchromenes.⁴⁸

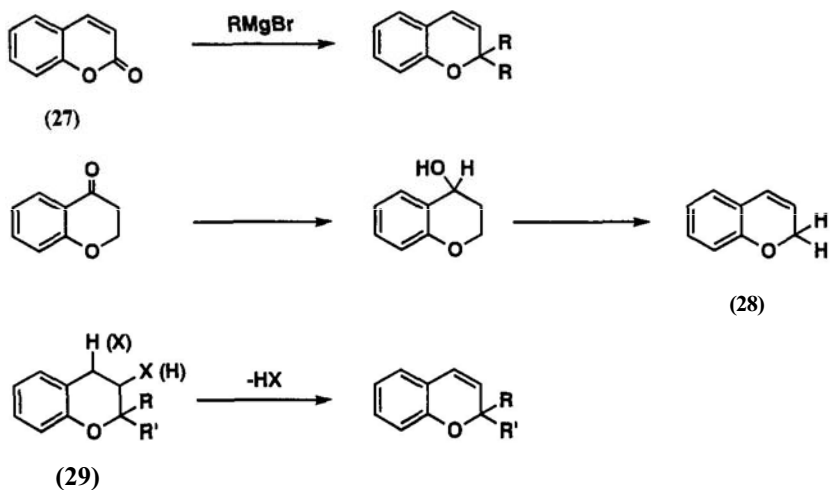
The 2,2-dialkylchromenes can easily be obtained from the reaction of coumarin **27** with a Grignard reagent.⁴⁸ This method has been known for a long time and has not been modified much. The parent chromene **28** has been prepared by reduction and dehydration of 4-chromanone.⁶³ Elimin-



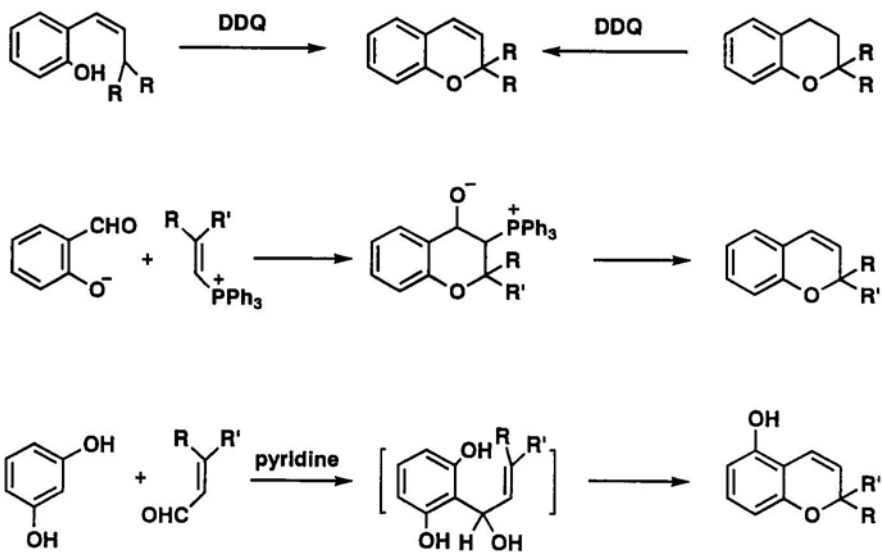
Scheme 13

ation of HX from 2,2-dialkyl-3- or 4-halochroman **29** by base also gives 2,2-dialkylchromenes⁶⁴ (Scheme 14).

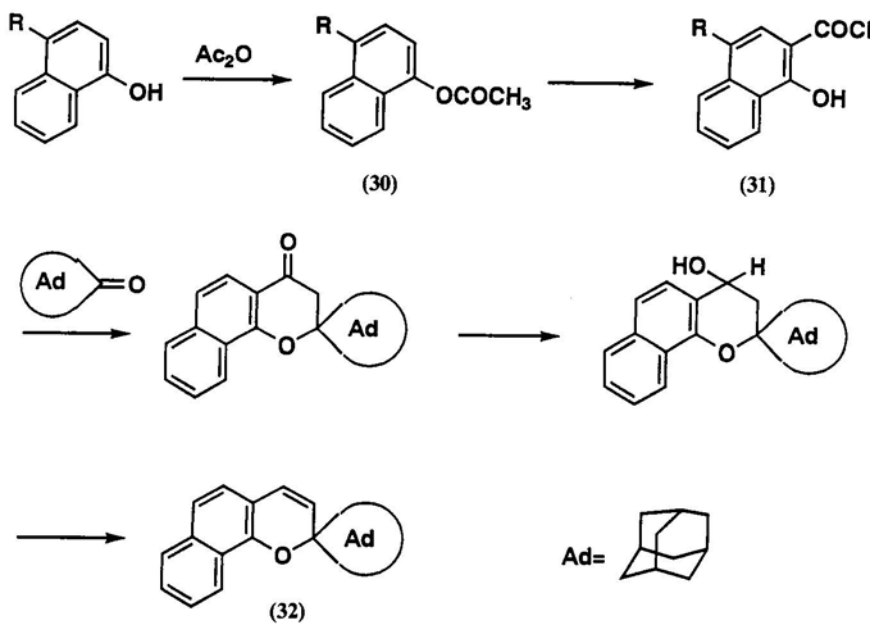
Oxidation of α,β -unsaturated (or β,γ -unsaturated) o-propenylphenol or 2,2-dialkylchroman with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gives chromene derivatives.^{65,66} 2,2-Dialkylchromene is also obtained by



Scheme 14



scheme 15



Scheme 16

the Wittig reaction from salicylaldehyde and vinylphosphonium salt,^{48,67} or by condensation of $\alpha\beta$ -unsaturated aldehydes with resorcinals in the presence of pyridine^{68,69} (Scheme 15).

The colored form of spironaphthopyran **32** absorbs at $\lambda_{\max}$ of ca. 450 nm,⁷⁰ and the closed spiro form is colorless, which has no absorption band above 400 nm. Bulky substituent group is especially important for photochromic sunglass. Introduction of the spiroadamantane or spirobicyclo[3.3.1]heptane into the 2-position of naphthopyran increases the resistance to photo-fatigue reaction, since endocyclic double bond induced by 1,7-hydrogen shift in the colored form cannot be formed in 2-adamanty1 or 2-bicycloheptany1 group.

Typical preparation of naphthopyran **32** involves Fries rearrangement of 1-acetoxynaphthalene **30**. Condensation of 2-acetyl-1-naphthol **31** with adamantanone, followed by usual reduction and dehydration gives **32** (Scheme 16).⁷⁰

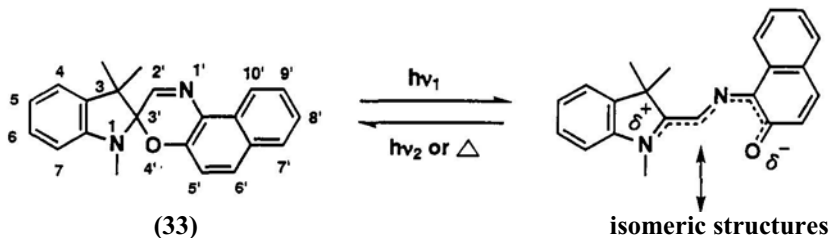
The colored form of 2,2-diphenyl-2*H*-thiochromene (thio analogue of chromene) absorbs at 650 nm in 3-methylpentane at 77 K.⁷¹

1.3. SPIRONAPHTHOOXAZINE

1.3.1. Introduction

Spirooxazine is an aza analogue of spiropyran in which the carbon atom at 3-position is replaced by a nitrogen atom. Historically, the photochromic phenomenon of spiroindolinoxazine derivatives was found after discovery of photochromic spiroindolinobenzopyran.⁷²

Spiro-naphtho-xazine **33** is commercially available as a photochromic compound. Due to its excellent lightfastness, many spiro-naphtho-xazines have been synthesized and their photochromic properties have been investigated for industrial applications. Spiro-naphtho-xazine is colorless ($\lambda_{\max} < 400$ nm), and its photomerocyanine form mainly gives blue color.



Scheme 17

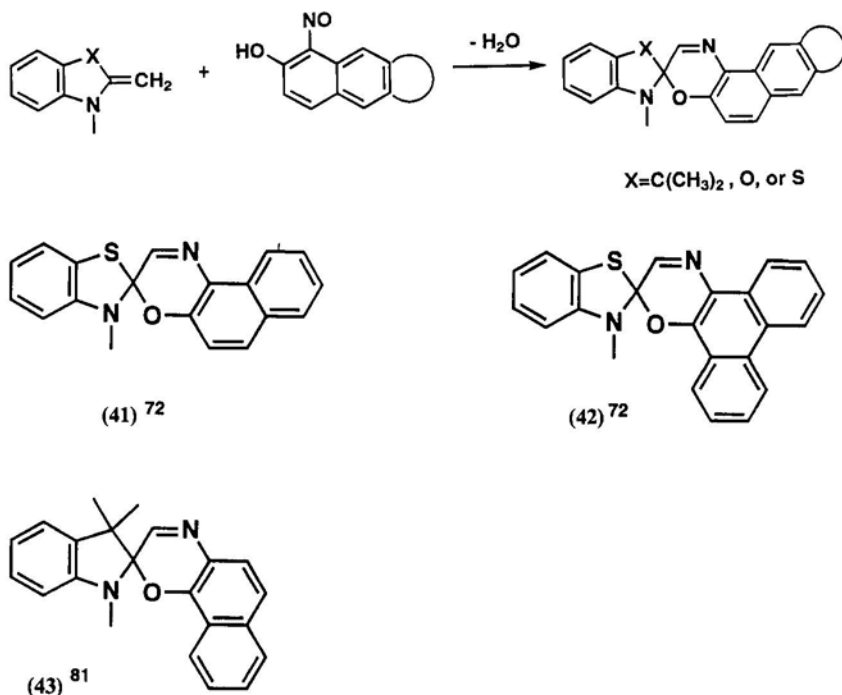
Very little is known about the parent benzoxazine analogue,¹ due to difficulties in the preparation of o-nitrosophenol. Synthetic procedures and practical application of spironaphthooxazines can be found in the patent literature and have been reviewed.⁷²

The name used by the *Chemical Abstracts* for spironaphthooxazine **33** is 1,3-dihydrospiro[2*H*-indole-2,3'-[3*H*]naphtho[2,1-*b*][1,4]-oxazine]. The numbering is shown in Scheme 17.

1.3.2. Synthesis

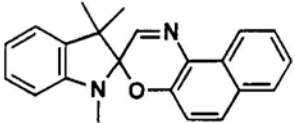
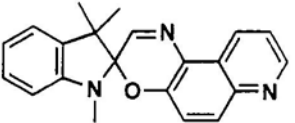
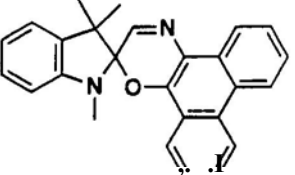
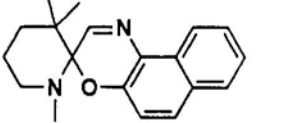
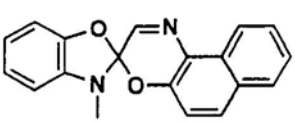
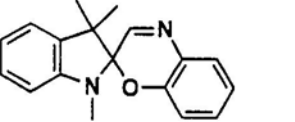
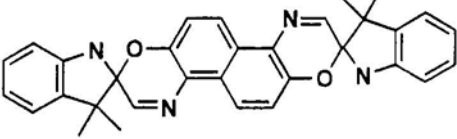
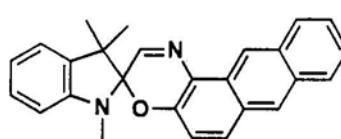
Spironaphthooxazines are generally prepared by condensation of 2-alkylidene heterocyclic compounds with an o-nitrosophenol in methanol or ethanol, as shown in Scheme 18.⁷³

o-Nitrosophenol is prepared by reaction of β -naphthol with sodium nitrite in aqueous solution.⁷⁴ Similarly, 5-nitroso-6-quinoline, 9-nitroso-10-phenanthrol, and other o-nitroso arylols useful for the preparation of spirooxazine derivatives, have been prepared.⁷² Only one absorption band (λ_{max} 500 nm) for the colored form of 1,3,3-trimethylspiroindolinobenzo-



Scheme 18

Table 5. $\lambda_{\max}$ of the Colored Form of the Spirooxazine Series in Toluene

 (33) 590 nm^{73,77,78}	 (34) 590 nm⁷⁸
 (35) 582 nm⁷⁹	 (36) 580 nm⁷²
 (37) 578 nm⁷²	 (38) 500 nm⁷³
 (39)^a 630 nm⁸⁰	 (40) 610 nm⁸²

^aIn PMMA film.

xazine **38** was listed in the previous review,¹ and other spectral data for this class are very limited. Other spiroindolinobenzoxazines from 3- or 5-methoxy-2-nitrosophenol or 3,3'-dinitroso-4,4'-dihydroxy diphenylmethane have been documented in the patents.^{75,76}

Indolines, benzoxazole, and benzothiazole are possible as 2-methylene heterocycles. The number of known spirooxazine derivatives is much less than for the spiropyran. This may be partly due to lack of many substituted o-nitrosophenols and partly due to lack of sufficient stability of spirooxazines. The structures of parent spirooxazines and the $\lambda_{\max}$ of their photomerocyanine forms are listed in Table 5. The $\lambda_{\max}$ of the colored forms of compounds **41–43** are not described in the literature.

Experimental Preparation of Spiroanththooxazine 33 (N-Bu). Triethylamine (3.54 g, 35 mmol) was added to a suspension of 2,3,3-trimethyl-*N*-butylindolinium iodide (12.0 g, 35 mmol) and *o*-nitrosonaphthol (6.1 g, 35 mmol) in EtOH (100 ml) under stirring. The mixture was refluxed for 2 h, cooled, and evaporated under reduced pressure. The residue was chromatographed on silica gel with benzene as an eluent, and then recrystallized from methanol to give spiro(*N*-butylindolinonaphthooxazine) **33** (6.6 g, yield 51%).

1.3.3. Absorption Spectra of Photomerocyanine Forms

The absorption band of the colored form of spiroanththooxazine has been measured in thermal equilibrium with the spiro form, particularly in a polar solvent at low temperature. Typical absorption spectra of the colorless and the colored form in polymer films are shown in Figure 1.8.

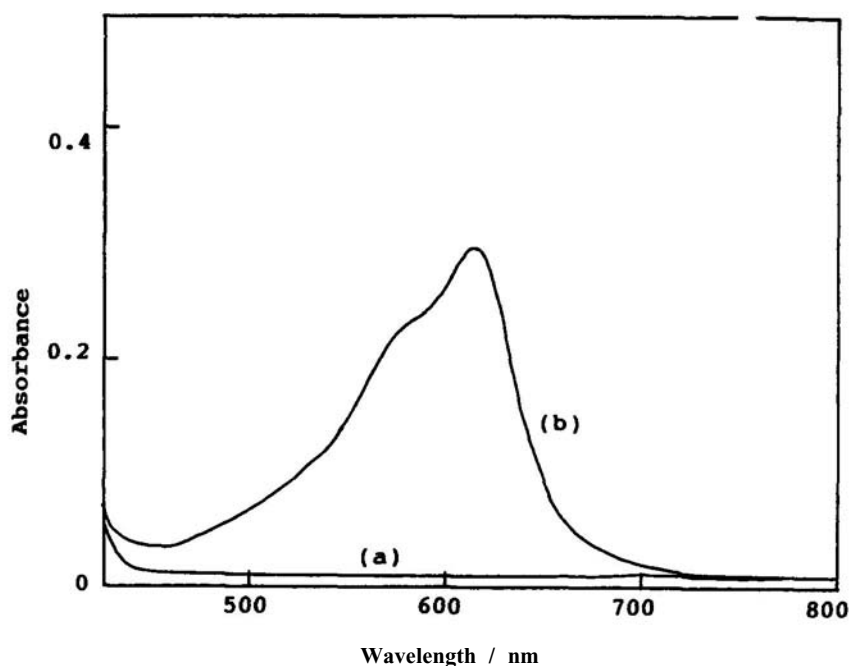


Figure 1.8. Absorption spectra of (a) the colorless form and (b) the colored form of 1-butyl-3,3-dimethyl-spiroindolinonaphthooxazine produced by irradiation with UV light in PVC film (1.0 wt%) at 23°C.

The thermal fading rate of the colored form can be stopped at low temperature (-60 to -75°C). For example, at -75°C the λ_{max} and molar absorptivity of the colored form of spironaphthooxazine **33** have been found experimentally to be 612 ($\epsilon = 8 \times 10^4 \text{ dm}^{-3} \text{ M}^{-1} \text{ cm}^{-1}$) and 578nm ($\epsilon = 4.9 \times 10^4 \text{ dm}^{-3} \text{ M}^{-1} \text{ cm}^{-1}$).⁷⁷

In contrast to normal spiropyrans, in spironaphthooxazine series, as the polarity of the solvent decreases, a hypsochromic shift of the λ_{max} of the colored form is observed, except for spiropiperidinonaphthooxazine.⁷⁹ For example, the λ_{max} of **33** shifts to shorter wavelength of ca. $20\text{--}60 \text{ nm}$ in less polar solvents, such as toluene and cyclohexane, compared to ethanol. This result may suggest that the ground state of the photomerocyanine form in spironaphthooxazine is less polar than the excited state and the neutral quinoid form largely contributes to the photomerocyanine form in the ground state.

The λ_{max} of **33** shows a bathochromic shift, compared to that of the corresponding spironaphthopyran [λ_{max} $531, 558(\text{s}) \text{ nm}$ in toluene].⁷⁸ The substituent effect in $2',5',6'$ - and 5 -position of **33** on the absorption band of the colored form has been examined.^{72,77,78} The donor substituent group in $6'$ -position, such as piperidino group, gives a hypsochromic shift by 35 nm , but $5'$ -carbomethoxy substitution results in a bathochromic shift by 20 nm . This may be due to interaction between oxygen atom of the phenolate and methoxy group.

Unlike spiropyrans, $2'$ -substitution in spirooxazine has no effect on λ_{max} . Alkoxy, chloro, and nitro substituents at 5 -position, and alkyl substituent at 1 -position in the indoline component have small effects on the λ_{max} of the colored form.

Extension of π -conjugation from naphthalene to anthracene and phenanthrene has a small effect on the λ_{max} of the photomerocyanine form. Replacement of the indoline ring with piperidine, benzoxazole, or benzothiazole⁸³ has resulted in hypsochromic shift by ca. 10 nm .⁷²

1.3.4. Photochromism and Thermochromism

Spirooxazines are generally colorless compounds whose absorption bands lie in the UV region, and show photochromism in solution, plastic resin, and films. The quantum yield of the photocoloration of spiroindolinonaphthooxazine in ethanol is very high (>0.90). In contrast to spiropyrans, the photocoloring reaction of spironaphthooxazine proceeds via an excited singlet state. For photocoloring reaction, photosensitization by benzophenone has not been observed. Recently, two stereoisomers (analogous to C and D in Figure 1.1) of the colored form are suggested based on

thermal fading Kinetics,⁷⁸ and detected by picosecond Raman and absorption spectroscopy technique.⁸⁴

The spiroindolinonaphthooxazine is generally very stable toward UV light, compared with spirobenzopyran. However, replacement of the indoline ring with benzoxazine significantly reduced its photostability.

Like other spiropyrans, the colored form of spirooxazines generated by UV irradiation, reconverts to the colorless form. However, it is possible to measure the thermal decay rates and activation energies at ambient temperature, since this fading reaction obeys first-order kinetics in solution. The thermal decay rate constant for spiroindolinonaphthooxazine has been found to be $0.02\text{--}0.15\text{s}^{-1}$ in ethanol and $0.1\text{--}1.4\text{s}^{-1}$ in toluene, although this may vary according to the substituent groups.^{72,77} However, these values are smaller than those of the spironaphthopyran series.

Colored forms of 5',8'-disulfonate derivatives of **33** chelate with divalent metal ions, e.g., Ca^{2+} , Cu^{2+} , and Pb^{2+} , causing blueshift.⁸⁵ The order of blueshift and thermal stability of the chelated photomerocyanine is as follows: $\text{Ca}^{2+} < \text{Cu}^{2+} < \text{Pb}^{2+}$. 5'-Methoxy derivative of **33** also gives Ni^{2+} complexes. This chelation significantly stabilizes photomerocyanine, compared with the nonchelating colored form. In contrast to sulfonate derivatives, chelation of 5'-methoxy derivatives with Ni^{2+} causes redshift (ca. 40 nm), but their structures are not clear.

Thermochromism of spiroindolinonaphthooxazine is observed only in high-concentration solution.⁷⁷ A high concentration (10^{-3} M) of **33** in ethanol produces a bluish solution, and its color intensity increases as the temperature of such concentrated solution increases. This thermal equilibrium is also affected by substituent groups. Donor substituent groups promote the formation of the colored form.

1.3.5. Applications

Spirooxazine compounds are useful in the field of plastic lenses, such as sunglasses and ski goggles. The plastic photochromic sunglasses have been in the marketplace since the early 1980s, and their market share is presently ca. 70%. The excellent lightfastness of the spironaphthooxazine series makes such applications possible, compared to other photochromic compounds.

Although spironaphthooxazines have excellent lightfastness, they decompose slowly on exposure to sunlight. However, lightfastness can be improved by addition of nickel stabilizers (singlet oxygen quenchers) or hindered amines (antioxidants).^{86–88}

Other applications of spirooxazine compounds include toys, cosmetics, printing inks, and clothes.

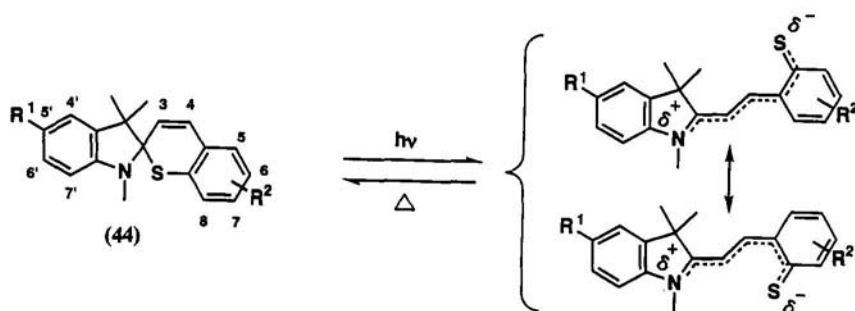
1.4. SPIROTHIOPYRAN AND RELATED COMPOUNDS

1.4.1. Molecular Design for the Near-IR Dyes

Becker and Kolc first examined the photochromism of spiroindolinobenzothiopyran **44**, a thio analogue of spiroindolinobenzopyran (Scheme 19). The closed form of this spirobenzothiopyran is stable and the photocoloration is very slow, compared with spiropyrans.⁷¹

In recent years, much effort has been focused on the development of new spirothiopyrans having absorption maxima of the colored form within the range of the oscillation wavelength of semiconductor lasers. The length of π -conjugation from nitrogen atom in the indoline component to sulfur atom of thiolate is fixed to make up the spiro skeleton and additional conjugation cannot be inserted to this main π -conjugation. Substituents that produce bathochromic shifts of the colored form are limited. However, 5',6-dinitro derivative gives the most bathochromic shift.^{13,89} Its colored form has the absorption maximum in the near infrared region, and is available for application in erasable optical data storage using a semiconductor laser (780–830 nm).

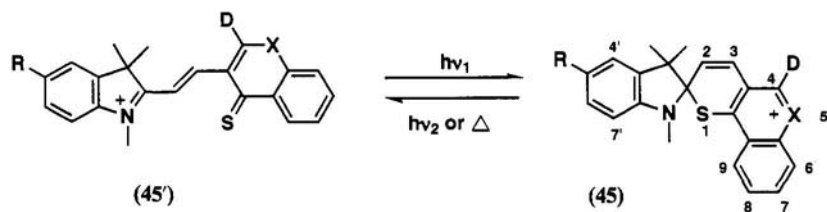
Another approach to shift absorption bands for the colored form is the extension of π -conjugation outside the spiro skeleton. Procedures of molecular designs for such photochromic compounds are shown in Scheme 20.



Scheme 19



scheme 20



For 45 and 45'	X	D	R
a	O	H	H
b	O	-CH=CH-NMe ₂	H
c	O	-CH=CH-NMe ₂	NO ₂
d	O	-CH=CH-C ₆ H ₄ - <i>p</i> -NMe ₂	H
e	O	-CH=CH-C ₆ H ₄ - <i>p</i> -NMe ₂	NO ₂
f	S	-CH=CH-C ₆ H ₄ - <i>p</i> -NMe ₂	H

Scheme 21

should be considered outside the spirothiopyran skeleton. For example, in compound **45a** (Scheme 21), the extension of π -conjugation is possible by introducing electron-donating substituent at positions 4 and 6 to 9 in the thiopyran component. (2) The absorption maxima of various colored forms with extended π -conjugation are calculated by PPP-MO. For example, in **45**, absorption maxima of merocyanine dyes with extended π -conjugation at 4-position calculated by PPP-MO are listed in Table 6. Merocyanine dyes **45e** and **45f** having calculated absorption band above 700nm are selected. (3) The preparation of these spirothiopyrans is planned.

The colored form of spiropyrans **10** presented in Table 3, which shows $\lambda_{\max}$ in the near IR, has been prepared using similar molecular design.¹³ In contrast to spiropyran **10**, the merocyanine form **45'** is unstable, and quickly changed to the spiro form **45**. The thermal stability is affected by presence

Table 6. PPP Calculation of Merocyanine Dyes **45b'**–**45f'**

Compounds	X	D	R	$\lambda_{\max}, \text{nm(f)}^a$
45b'	O	—CH=CH—NMe ₂	H	566(0.39)
45d'	O	—CH=CH—C ₆ H ₄ - <i>p</i> -NMe ₂	H	690(1.11)
45e'	O	—CH=CH—C ₆ H ₄ - <i>p</i> -NMe ₂	NO ₂	718(0.95)
45f'	S	—CH=CH—C ₆ H ₄ - <i>p</i> -NMe ₂	H	727(1.36)

^aOscillator strength.

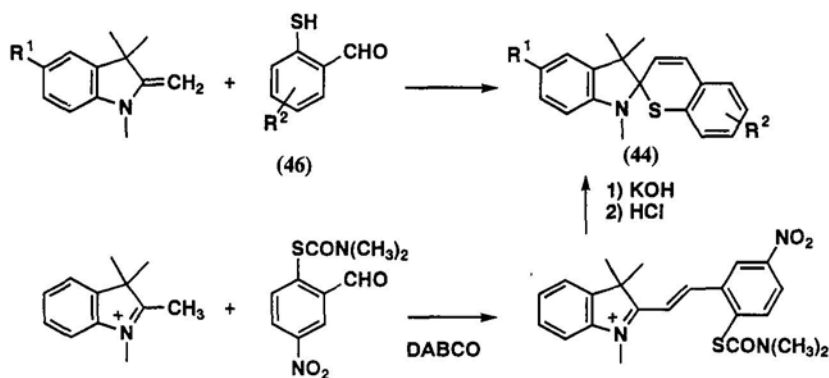
of a nitro group. Compounds **45c** and **45e** include a nitro group in the indoline component, and no longer exhibit photochromic behavior at room temperature.

With the help of similar molecular design, spirothiopyranonaphthopyrans **19** with absorption band in the near IR (692–850nm) on UV irradiation have been prepared.⁵² As predicted, the photocoloration of these spirothiopyrans occurs, but the reverse reaction to colorless form does not occur in solution as extension of π -conjugation increases.

1.4.2. Synthesis

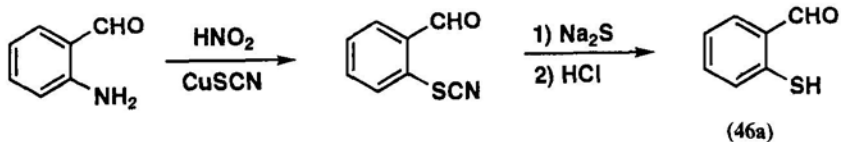
Spiroindolinobenzothiopyrans can be prepared by condensation of Fischer's base with thiosalicylaldehyde derivatives **46** in ethanol, as shown in Scheme 22.^{71,89,93} Reaction of 1,2,3,3-tetramethylindolinium salt with carbamoylthiobenzaldehyde,⁹² which is an intermediate for preparation of thiosalicylaldehyde, also gives the spirobenzothiopyran in high yield via the corresponding indolinium salt, as shown in Scheme 22.⁹⁴ Conversion of spirobenzopyrans to the corresponding spirobenzothiopyran by phosphorous pentasulfide in pyridine or xylene is possible, but the purification of the product is difficult.

Although thiosalicylaldehyde **46a** ($R^2 = H$) was first synthesized by Friedlander and Lenk (Scheme 23),⁹⁵ it is an unstable intermediate and should be stored in solution below 0°C. Alternate synthetic procedures utilizing o-chlorobenzaldehyde or salicylaldehyde, as starting materials, are shown in Scheme 24.⁹⁶ The preferred method for the synthesis of substituted thiosalicylaldehydes **46** is via salicylaldehyde.

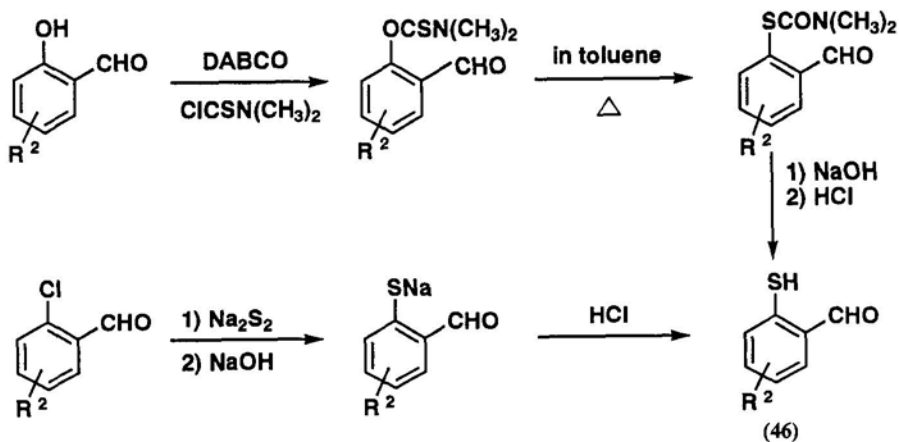


DABCO:1,4-diazabicyclo[2.2.2]octane

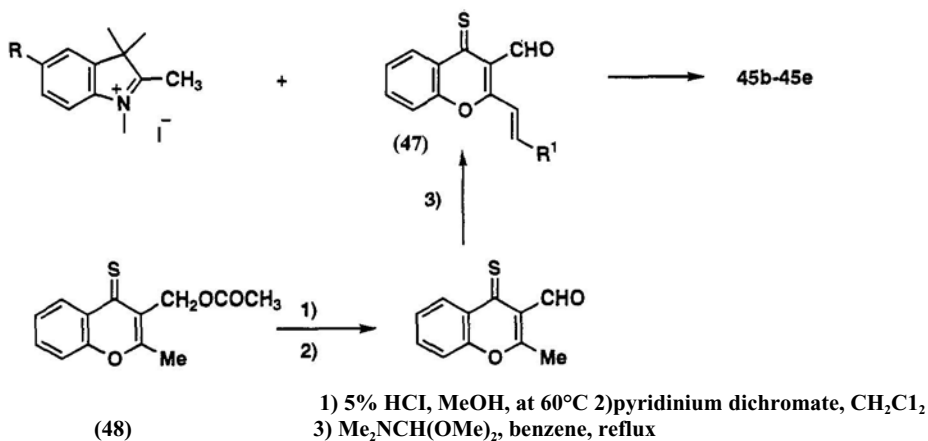
Scheme 22



Scheme 23



Scheme 24



Scheme 25

Spirothiopyrans **45b** including a benzopyrylium ring have been prepared in one step by condensation of 2-aminovinyl-3-formylchromone-4-thione **47** with 1,2,3,3-tetramethylindolinium salts in ethanol (Scheme 25).⁹⁰ The precursor **47** is prepared from 3-carboxymethylene-2-methyl-chromone-4-thione **48**. First, oxidation of **48** with pyridinium dichromate in CH_2Cl_2 , and then condensation with dimethyl formamide dimethyl acetal in benzene gave compound **47**.

Experimental Preparation of 5',6-dinitrospirobenzothiopyran 44b. A mixture of 5-nitro-1,3,3-trimethyl-2-methyleneindoline (0.38 g, 1.75 mmol) and 5-nitro-thiosalicylaldehyde (0.22 g, 1.2 mmol) in EtOH (50 ml) was refluxed for 2h, and then evaporated under reduced pressure. The residue was chromatographed on silica gel with benzene–acetone (15:1, v/v) and recrystallized from dichloromethane–hexane to give **44b** ($\text{R}^1 = \text{NO}_2$, $\text{R}^2 = 6\text{-NO}_2$)(0.30 g, yield 65%).

Preparation of Spirothiopyranobenzopyrylium iodide 45b. A mixture of 2,3,3,4-tetramethylindolinium iodide (0.090 g, 0.3 mmol) and 2-(*N,N*-dimethylaminovinyl)-3-formyl-chromone-4-thione **47** [$\text{R}^1 = \text{N}(\text{Me})_2$] (0.086 g, 0.33 mmol) in EtOH (10 ml) was refluxed for 1 h. After cooling, the reaction mixture was poured into 100 ml of ether. The precipitate was filtered off and dispersed in 50 ml of ether with stirring for 15 min, followed by filtration. Repeating this procedure gave a pure spirothiopyranobenzopyrylium iodide **45b** (0.13 g, yield 80%).

1.4.3. Physical Properties

Though the colored form of unsubstituted spirobenzothiopyran is unstable, the nitrosubstituent leads to stabilization of the colored form. The absorption maxima of some 6-nitrospiroindolinobenzothiopyrans **44** in a

Table 7. Absorption Maxima of the Colored Form of Spiroindolinobenzothiopyran **44** in Vinyl Chloride–Vinylidene Chloride Copolymer

R^1	R^2	$\lambda_{\text{max}}, \text{nm}$
H	6- NO_2	680
Cl	6- NO_2	690
NO_2	6- NO_2	750
OCH_3	6- NO_2	660
OCH_3	6- NO_2 , 8- OCH_3	690
OCH_3	6- NO_2 , 8-Cl	650

polymer film have been measured (Table 7).⁸⁹ The absorption spectra of the colorless and colored form of 6-nitrospiroindolinobenzothiopyran are shown in Figure 1.9. The colorless form does not have absorption bands in the visible region, and the colored form has a broad band in the near infrared region indicating the absorption band significantly shifts to longer wavelength, compared to spirobenzopyran.⁹³

Substituent effects on the $\lambda_{\max}$ are remarkable. Electron-withdrawing groups at the 5'-position, e.g., 5'-nitro-substitution (indoline component), and donor substituent at the 8-position (benzothiopyran component) in **44** leads to a longer wavelength shift. As the polarity of the solvent increases, the $\lambda_{\max}$ of the colored form of spiroindolinobenzothiopyran results in hypsochromic shift. This can be interpreted as the existence of a polar structural component of the colored form in the ground state. Kinetic study has suggested that the zwitterionic structure largely contributes to the colored form of 6-nitrospiroindolinobenzothiopyran, as well as spiropyrans.⁹⁷ Based on ¹H-NMR and X-ray analysis,^{98,99} the existence of an

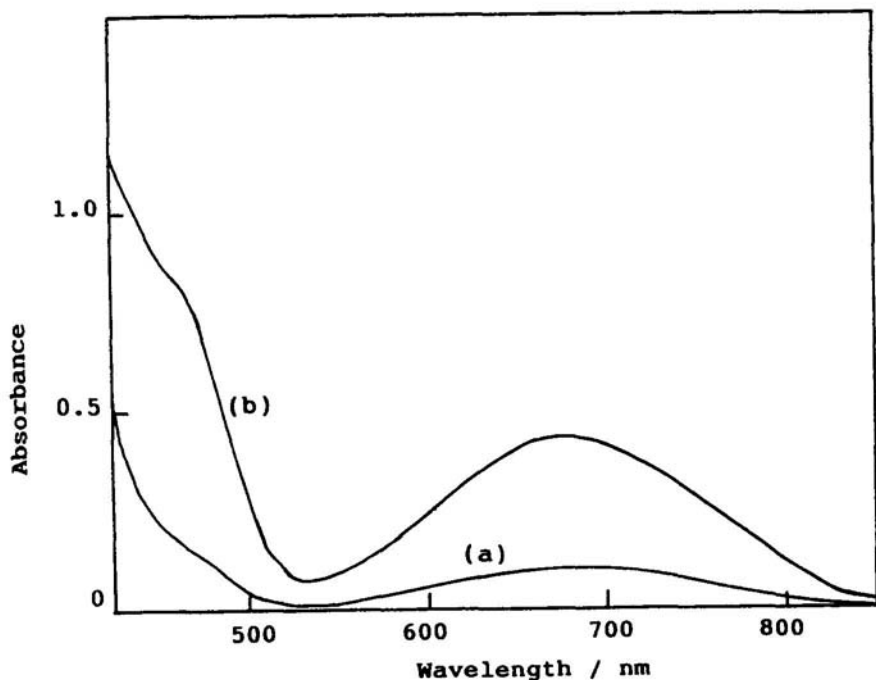


Figure 1.9. Absorption spectra of (a) the colorless form and (b) the colored form of 1'3',3'-trimethyl-6-nitrospiroindolinobenzothiopyran **44a** ($R^1 = H$, $R^2 = 6\text{-NO}_2$) produced by irradiation with UV light in PVC film (1.0 wt%) at 23°C.

equilibrium mixture of *trans-cis* and *trans-trans* isomers for the colored form of 8-methacryloxymethylspiroindolinobenzothiopyran is proposed.

In the spirothiopyran **45b**, the spiro form has two absorptions in the visible region (λ_{max} 490 and 474 nm) due to a polyene chromophore from *N*-vinyl group to oxygen of the benzopyrylium component.⁹⁰ The colored form of **45b** produced by visible light irradiation shows the λ_{max} at 570 nm. This colored form **45b'** was confirmed by characteristic ¹H-NMR spectra, as well as that of spirothiopyran.

Quantum yields of the coloration of spiroindolinobenzothiopyran are very small, compared to those of the spirobenzopyrans. For example, for 6-nitro-8,5-dimethoxyspiroindolinobenzothiopyran the quantum yield is 0.048 in EtOH, and 0.018 in DMF.¹⁴ The mechanism of photocoloration of spiroindolinobenzothiopyrans involves the excited singlet state, but not the excited triplet state, as shown from experiments using ferrocene as a triplet quencher. The low quantum yield may be due to deactivating influence of sulfur atom in **44**. Nevertheless, **44** follows the same mechanism as that of normal spirothiopyran. The thermal fading rate constant at 25°C (conversion from the colored form to the spiro form) is 10^{-1} to 10^{-4} s⁻¹ depending on the solvent. A repeat of 30 cycles of photothermochromism was required to achieve 50% photodegradation in degassed DMF.⁹⁷

The structures of some spiroindolinobenzothiopyrans have been determined by X-ray crystallography. Selective bond lengths of spirothiopyrans

Table 8. Selected Bond Length (Å)
of Spirothiopyrans **44a** (R¹ = H,
R² = 6-NO₂) and **45b**

Bond	44a ^a	45b ^a
N1—C2	1.45	1.52
N1—C8'	1.40	1.49
C2—C3'	1.58	1.51
C3'—C9'	1.48	1.57
C8'—C9'	1.39	1.35
C2—C3	1.50	1.55
C3—C4	1.33	1.23
C4—C10 ^b	1.44	1.43
C9—C10 ^b	1.40	1.39
S1—C9 ^b	1.76	1.67
S1—C2	1.89	1.87

^aEstimated standard deviations for **44a** and **45b** are 0.01 and 0.02–0.03 Å, respectively.

^bNumbering for compounds **45b** is C4—C12, C11—C12, and S1—C11.

44a (**44**: $R^1 = \text{H}$, $R^2 = 6\text{-NO}_2$) and **45b** are listed in Table 8 and their PLUTO figures are shown in Figure 1.10.91

The C—S bond length (1.87 or 1.89 Å) between the sulfur and the spiro carbon in both spirothiopyrans is longer than found for the nonconjugated C—S bond (1.77 Å), and longer than normal C—S bonds in benzothiopyrans. The nitro-substituent in the indoline component affects the structure of spirothiopyrans. In the series of spirobenzothiopyrans **44**, the double bond length (C3—C4) in the thiopyran ring for 5'-nitro derivative **44b** (**44**: $R^1 = \text{NO}_2$, $R^2 = 6\text{-NO}_2$) becomes shorter (0.08 Å) and the N1'—C8' bond length becomes shorter (0.03 Å). On the other hand, in a

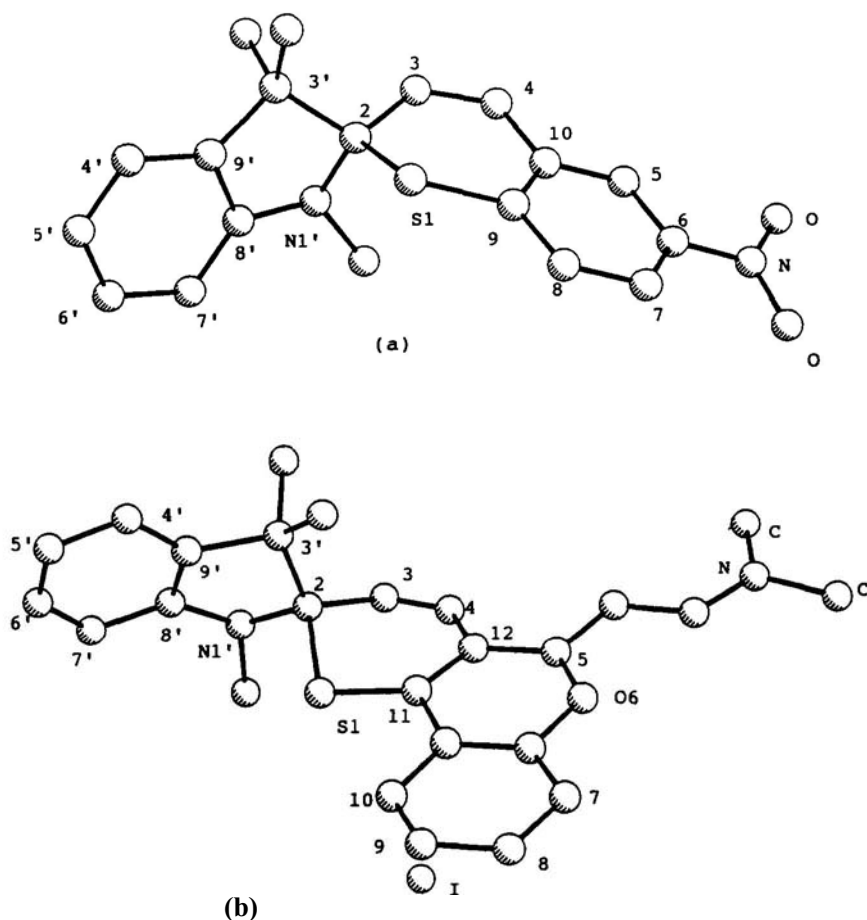


Figure 1.10. PLUTO views and numbering of spiro compounds: (a) **44a**; (b) **45b**.

Table 9. Deviations from the Optimum Plane 1 in **44a** and **44b**

		Deviations (Å) ^a	
		44a (R ¹ = H, R ² = 6-NO ₂)	44b (R ¹ = NO ₂ , R ² = 6-NO ₂)
Plane 1	C2	0.223	-0.152
	C3'	-0.194	0.149
	C9'	0.061	-0.071
	C8'	0.084	-0.020
	N1	-0.134	0.095
	means	0.139	0.097

^aEstimated standard deviations: 0.005–0.009 Å.

series of spirothiopyrans **45**, this substituent effect leads to shorter N1'–C8' bonds.

The heterocyclic rings in the indoline component in **44** and **45** are not planar, but the deviations from the optimum planes of this heterocyclic ring are affected by nitro substituents. This deviation in 5'-nitro derivative **44b** is smaller, compared with **44a** as shown in Table 9. The dihedral angles between the indoline ring (plane 1) and benzene ring (plane 2) fused to the indoline ring are 7.31° and 2.05° for **44a** and **44b**, respectively, indicating an increase in planarity of the indoline component due to the nitro substituent in **44**. In the spirothiopyran series **45**, similar increase in this planarity is observed since the means deviation from the plane of the indoline ring (plane 1) decreases from 0.143 Å to 0.122 Å and the dihedral angle between the indoline ring and the benzene ring fused on the plane 1 ring also decreases from 9.55 to 6.09°.

1.4.4. Applications

Due to the absorption band of the colored form of spiroindolinobenzothioopyrans in the near IR region, they have been used in the optical erasable recording disks.^{89,100,101} The principle of optical erasable recording system using photochromic spirobenzothioopyran is explained as follows.

First, the recording layer which contains photochromic spirobenzothioopyran in liquid-crystal polymer or polymer such as vinyl chloride–vinylidene chloride copolymer, is made colored by UV irradiation. In the recording (writing) process, a colorless recording dot in the recording layer is formed by semiconductor laser beams (789 nm, 15–20 mW).¹⁰⁰ This process is essentially thermal decoloration of the photomerocyanine form by laser beam.

In the reproducing (reading) process, the presence of the colorless form is detected by difference in reflectivity using the same laser beam at weak power (1 mW), and the signal is picked up by photodiode. In reversible process, the nonrecording area again was obtained by UV irradiation. Practically, in such optical disks using spirothiopyran, an S/N of 54 dB was detected.^{89,100}

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2

Leuco Quinone Dyes

MASARU MATSUOKA

2.1. INTRODUCTION

The chemistry of quinone dyes has been discussed in a series of books entitled *The Chemistry of Synthetic Dyes*, edited by Venkataraman.¹ The general chemistry of quinoid compounds has been discussed by Patai.² There have been many books that cover quinoid compounds as dyes and pigments but very few discuss the chemistry of the corresponding leuco dyes. Traditional vat dyes are applied to cellulosic fiber in the leuco form. The chemistry of the leuco form of vat dyes is rather simple. Some leuco quinones are quite stable in the solid state and can be stored for a year. Other leuco dyes are unstable in solution and gradually undergo aerial oxidation.

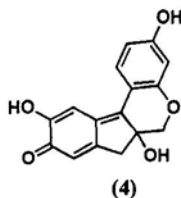
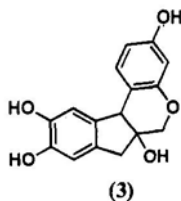
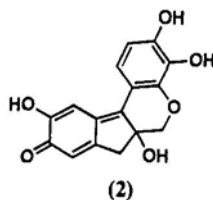
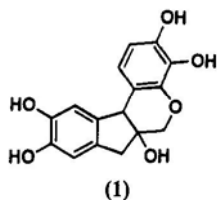
In recent years advances in the chemistry of leuco dyes have taken place particularly in the areas of structural identification by means of ¹H- and ¹³C-NMR and selective syntheses of aminoquinones, etc. New applications of leuco quinones such as in electro-optical devices and information recording media have enhanced their importance. In these applications, the chemistry of leuco quinones is interesting mainly due to switching from a colored to a colorless system by a redox process.

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Chemistry and Applications of Leuco Dyes, edited by Muthyala. Plenum Press, New York, 1997.

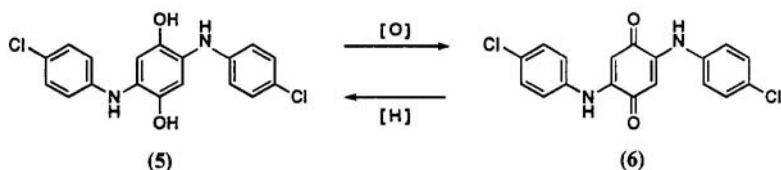
2.2. NATURAL LEUCO QUINONE

The most valuable colorless naturally occurring hydroquinone is hematoxylin (1)³ which is extracted from logwood, native to Central America. Compound 1 absorbs at 298nm in methanol but is rapidly oxidized by atmospheric oxygen and converts to hematein (2) which contains a *para*-quinoidal chromophore. Compound 1 is white in the pure state, turning yellow in air before undergoing further oxidation to a dark-colored material. The color of naturally occurring hematoxylin is due to the presence of hematein as an impurity. Compound 2 forms chelates with various metals giving a range of colors from reddish-violet, blue to black depending on the metal (C.I. Natural Black 1 and 2). Compound 1 is an excellent nuclear stain; several thousand pounds of this dye are used worldwide each year in biological-stain applications. A similar hydroquinone is brazilin (3) which is also oxidized to brazilein (4) (C.I. Natural Red 24). Naturally occurring quinones have been summarized by Venkataraman.⁴

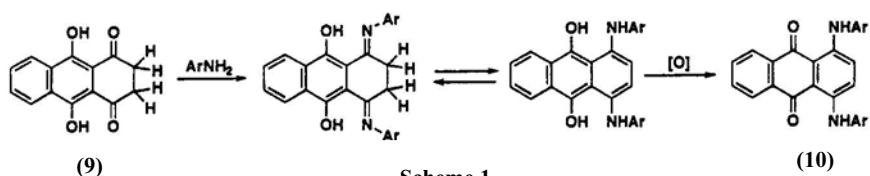
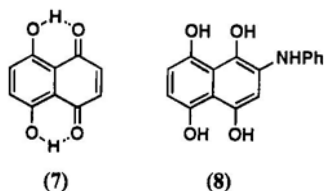


2.3. TRADITIONAL LEUCO QUINONE DYES

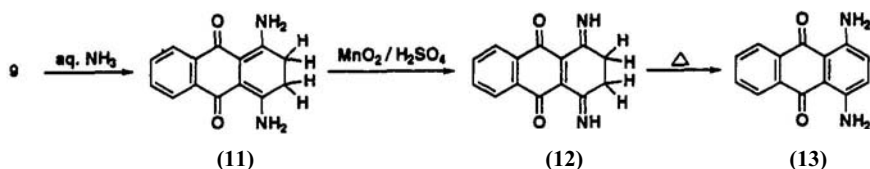
In the past, various leuco benzoquinone dyes⁴ were used as mordant dyes but recently they have been displaced by the azo mordant dyes. The reaction of *p*-benzoquinone with *p*-chloroaniline gives the hydroquinone derivative (5). Compound 5 undergoes oxidation to the corresponding benzoquinone 6. A mixture of hydrosulfite and compound 6 is marketed as a sulfurized vat dye which gives brown and khaki colors.



In the naphthoquinone series, naphthazarin (**7**)⁵ had considerable commercial importance at one time. Reduction of **7** gives 1,4,5,8-tetrahydroxynaphthalene (naphthazarin leuco form) which has been used to dye wool and silk from the leuco form. After oxidation of the leuco form with a metal ion such as chromium, a chelated dye is obtained giving a neutral black with good all-around fastness. Naphthazarin readily reacts with amines and phenols. Many mordant dyes such as Alizarin Black SRA (**8**) have been synthesized from naphthazarin. While these naphthoquinone dyes are of little technical importance, the leuco quinizarin (**9**) is an important intermediate for the synthesis of 1,4-disubstituted anthraquinone dyes. The reaction of **9** with arylamine followed by oxidation gives 1,4-bis(aryl-amino)anthraquinones (**10**) (Scheme 1).⁴ Interestingly, when **9** is heated with aqueous ammonia, only 1,4-diamino-2,3-dihydroanthraquinone (**11**) is formed. Oxidation of **11** with manganese dioxide leads to **12**, which on heating at about 100°C isomerizes to 1,4-diaminoanthraquinone (**13**) (Scheme 2).⁴



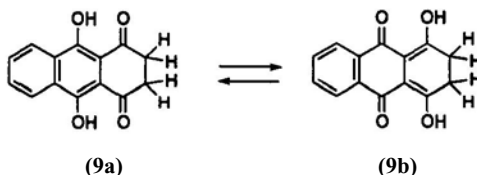
Scheme 1



Scheme 2

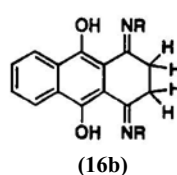
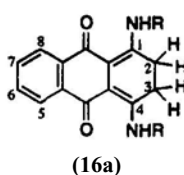
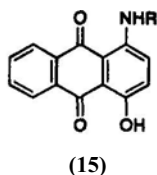
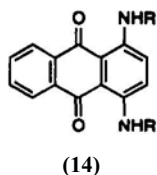
2.4. STRUCTURE OF LEUCO QUINONES

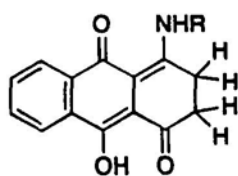
In 1963, Bloom and Hutton suggested⁵ the structure of leuco quinizarin in solution as 9,10-dihydroxy-2,3-dihydro-1,4-anthraquinone (**9a**). In 1981, Kikuchi and colleagues⁶ confirmed the structure by means of ¹H- and



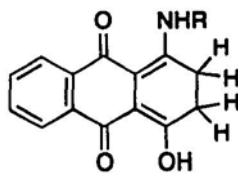
¹³C-NMR. The structures of the leuco derivatives of 1,4-bis(butylamino)-anthraquinone (**14**) and 1-butylamino-4-hydroxyanthraquinone (**15**) have been shown to be 1,4-bis(butylamino)-2,3-dihydroanthracene-9,10-dione (**16a**) and 1-butylamino-10-hydroxy-2,3-dihydroanthracene-4,9-dione (**17a**), respectively. On the other hand, leuco-1,4-dimethoxyanthraquinone has been assigned the structure, 1,4-dimethoxy-9,10-dihydroxyanthracene (**18**).

In proton NMR, 1,4-disubstituted anthraquinones show aromatic protons (5,8- and 6,7-positions) as A₂B₂ type, and the other aromatic proton signals (2,3-positions) as A₂ or AB type. Proton NMR data of leuco-1,4-disubstituted anthraquinones in deuteriochloroform are given in Table 1. Leuco-1,4-dimethoxyanthraquinone (**18**) has hydroxy protons (2H) exhibiting a singlet, at 9.78 ppm. As expected, aromatic protons appear as A₂B₂ and A₂ type. On the other hand, leuco-1,4-bis(butylamino)anthraquinones (**16**, R = *n*-Bu) do not show an A₂-type peak for 2,3-aromatic protons but rather a sharp singlet at 2.70 ppm. The *p*-quinoid structure for **16a** has been assigned based on ¹³C chemical shift of the carbonyl group, observed at 172.2 ppm (Table 2).

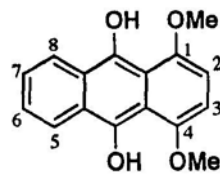




(17a)



(17b)



(18)

In the proton NMR spectrum of leuco- 1-hydroxy-4-butylaminoanthraquinone (**17**) a triplet at 2.88ppm due to the methylene protons (4H), a sharp singlet at 13.95ppm corresponding to one hydroxy proton, and a broad signal at 14.90ppm from one amino proton have been observed. These results permit the structural assignment of **17** to **17a** and **17b**.

Two structures **9a** or **9b** are possible for leuco quinizarin (**9**). Bloom and Hutton⁵ have proposed the structure of **9** to be **9a** by comparing the chemical shift of methylene protons with those of leuco naphthazarin (3.05 ppm) and leuco naphthoquinone (3.08 ppm). However, based on UV spectra and chemical reactivity, Egerton and CO-workers⁷ and Greenhalgh⁸ independently suggested an equilibrium mixture of **9a** and **9b** in solution.

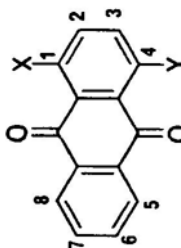
The ¹³C NMR spectral data for **9**, **16**, and **17** are shown in Table 2. The chemical shifts of carbonyl carbons of anthraquinones are characteristically observed at about 180 ppm.⁹ The chemical shifts for carbonyl carbons of 1,4-naphthoquinone and 1,4-benzoquinone appear at about 185 ppm, while those of carbonyl carbons adjacent to a methylene or methyl carbon are at about 200 ppm. The chemical shifts of the C1 and C4 of **9** are observed at 200.8 ppm and assigned to the 1,4-diketo form **9a**. In the ¹³C spectrum of **17**, the chemical shifts of carbonyl carbons are at 199.9 and 172.2 ppm. The former value corresponds to a carbonyl carbon adjacent to the methylene carbon, and the latter corresponds to the carbonyl carbon in the 9-position. The methylene carbons of **17** show two signals at 34.5 and 23.8ppm. From these results, **17** is considered to exist exclusively as an unsymmetrical 4,9-diketo form, **17a**. Thus, these NMR spectral data suggest

Table 1. ¹H-NMR Chemical Shifts of Leuco Anthraquinones⁶

Compound	(C-5.8	C-6.7	CH ₂	NHBu	OH	OMe
9	8.42	7.77	3.05(s)	—	13.50	—
16 (R = <i>n</i> -Bu)	8.42	7.58	2.70(s)	14.32	—	—
17 (R = <i>n</i> -Bu)	8.36	7.62	2.88(t)	14.90	13.95	—
18	8.30	7.40	—	—	9.18	3.93

Table 2. ^{13}C -NMR Chemical Shifts of Leuco Anthraquinones⁶

Compound ^a	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14
9	200.8	35.7	35.7	200.8	124.4	130.4	130.4	124.4	154.9	154.9	107.3	107.3	129.1	129.1
16 (R = <i>n</i> -Bu) ^b	162.1	22.9	22.9	162.1	125.7	129.9	129.9	125.7	172.2	172.2	102.2	102.2	135.7	135.7
17 (R = <i>n</i> -Bu) ^b	165.1	23.8	34.5	199.9	124.4	130.1	129.6	125.7	153.0	172.2	107.3	101.8	129.9	135.2

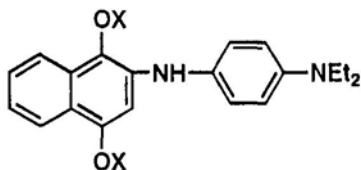
^aNumbering system of anthraquinone ring as follows:^bThe *n*-butyl group was observed as follows: (**16**) 13.9, 20.3, 31.9, 43.2 ppm; (**17**) 13.6, 20.1, 31.6, 43.6 ppm.

that the structures of leuco anthraquinones may differ depending on the substituents, e.g., **9** as 1,4-quinone, **16** as 9,10-quinone, **17** as 4,9-quinone, and **18** as 9,10-dihydroxyanthracene structures.

2.5. SYNTHESIS OF LEUCO QUINONES

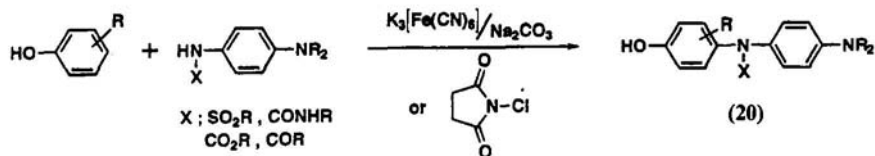
Anthraquinone leuco dyes are widely known as vat dyes.¹⁰ Vat dyes possess extensively conjugated aromatic systems containing two or more carbonyl groups, e.g., anthraquinone, indigoid chromophores. The colored form of vat dyes are insoluble in water. The dyes are applied by a process whereby the dye is converted to the reduced form (leuco dye) which is soluble in water and can penetrate into a cellulosic fiber. On exposure to the atmosphere the leuco form is oxidized to the original quinoid form which then precipitates as an aggregate. Vat dyes generally have excellent chemical and photochemical stability.

Leuco quinones can be synthesized by two methods, reductive trapping and oxidative coupling. A variety of reagents, e.g., SnCl_2 , Fe, dithionite, can be used for the reduction. The most general method has been reduction of quinone with reducing agents such as sodium dithionite in alkaline conditions under nitrogen atmosphere. Alternately, reduction of quinones with tin(II) chloride in aqueous hydrochloric acid gives leuco quinones. However, these leuco hydroxy compounds are unstable in air and their isolation requires protection of phenolic groups. Acylation is commonly used for the stabilization. The leuco naphthoquinone **19a** is unstable and is rapidly reoxidized to the quinone in air, but the benzoyl ester **19b** is quite stable and may be isolated and stored.¹¹ Leuco quinoneimine dyes **20** can be synthesized by oxidative coupling of phenols with arylamines in the presence of moderate oxidizing agents such as potassium ferricyanide in alkaline conditions.^{12,13}

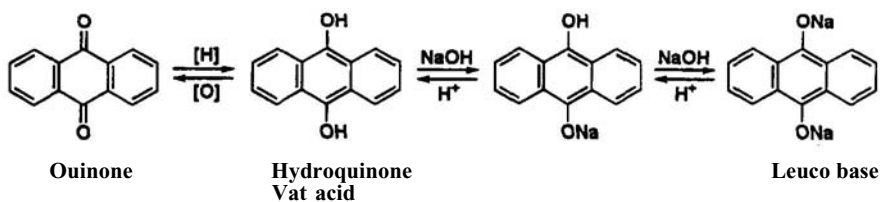


(19) **a**, X = H
b, X = C(=O)Ph

The leuco quinoneimine dyes are unstable to isolate but the substitution of an electron-withdrawing group such as acyl,¹³ carbamoyl,¹³ carboxy,¹³ or arylsulfonyl¹² group at the amino nitrogen atom stabilizes the



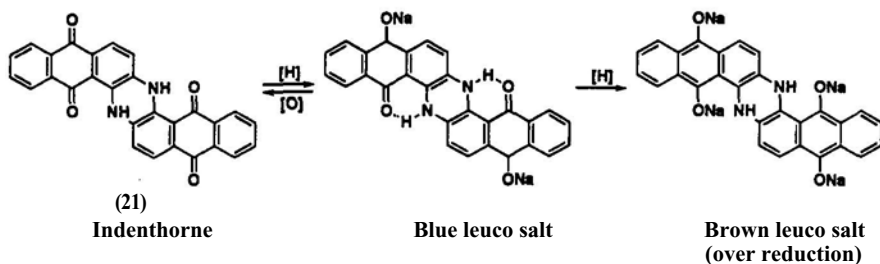
Scheme 3



Scheme 4

leuco form which then can be isolated in a stable state. The general syntheses of the leuco indophenol dyes are shown in Scheme 3.

Redox behavior of anthraquinone is shown in Scheme 4. The quinone moiety may be reduced to the hydroquinone form and converted to a leuco salt under alkali conditions. In general, the leuco salt has a strong affinity for cellulose and is soluble in water. The hydroquinone form is insoluble in water and has low affinity to cellulose. The preferred dyeing procedure depends on the structure and properties of the vat dye. The variables that are used to control the process include, e.g., strength and amount of alkali, reduction temperature, and the presence of salts. During the process of reduction, some side reactions, such as overreduction, hydrolysis,

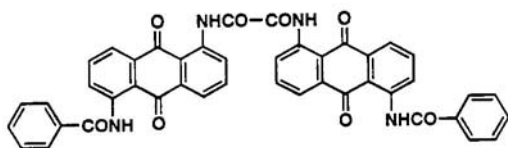


Scheme 5

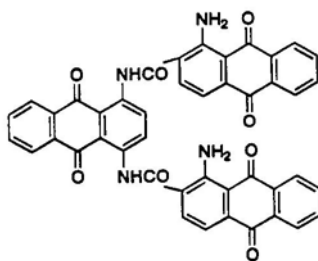
saponification of amido groups, dehalogenation, and keto–enol isomerism, are possible. Premature crystallization of leuco salt is undesirable during dyeing. These side reactions should be avoided to achieve good dyeing performance of vat dyes. Overreduction of indanthrone (**21**) produces brown leuco salt which has poor affinity compared with that of blue leuco salt (Scheme 5).

2.6. COMMERCIAL ANTHRAQUINOID VAT DYES

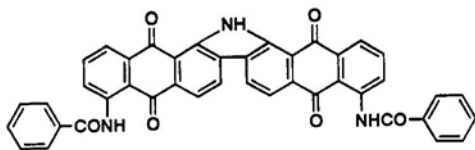
Indigo is the most important vat dye, dating back to ancient times and produced on an industrial scale since 1880. To replace the indigo dyes, the indanthrone (**21**) class of dyes was developed. Indanthrone has superior characteristics as a vat dye and became a key material for further development of anthraquinoid vat dyes. There exist a variety of anthraquinone vat dyes differing in the chromophoric system. The color–structure relationship of vat dyes have been rationalized by the Pariser–Parr–Pople molecular orbital (PPP MO) method. Some examples of commercialized anthraquinoid vat dyes are shown in Scheme 6.¹⁴



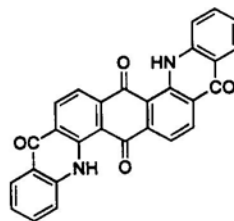
C.I. Vat Yellow 12



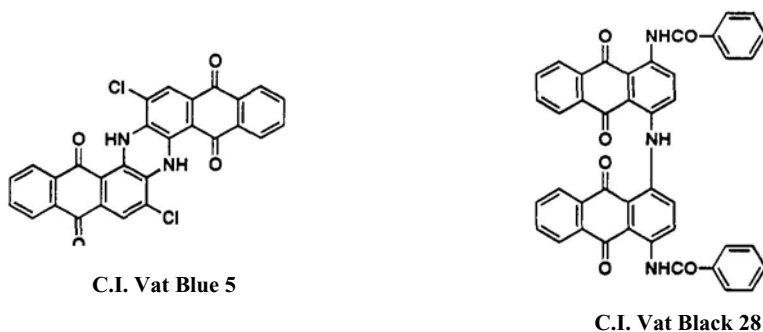
C.I. Vat Red 21



C.I. Vat Orange 15



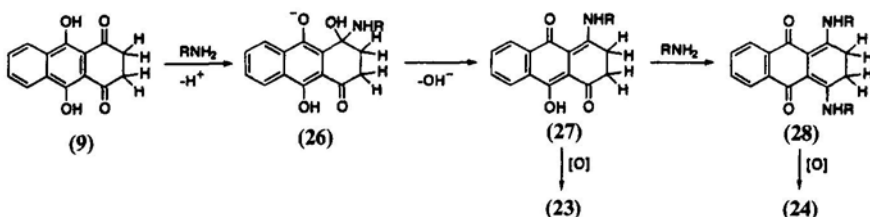
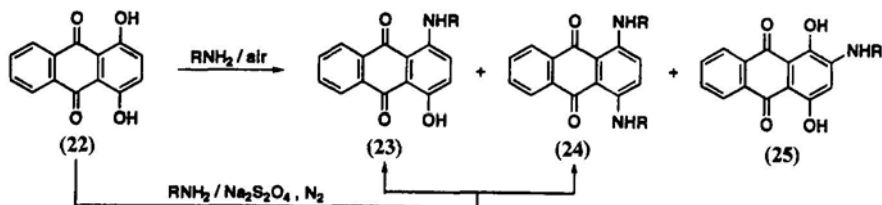
C.I. Vat Violet 13



Scheme 6

2.7. REACTION OF QUINONES

It is well known that quinizarin (**22**) is alkylaminated in air to give a mixture of 1-alkylamino-4-hydroxyanthraquinone (**23**), 1,4-bis(alkylamino)-anthraquinone (**24**), and 2-alkylaminoquinizarin (**25**) (Scheme 7). The reaction conditions affect the ratio of these products. In a nitrogen atmosphere, or in the presence of sodium dithionite as reducing agent, the main amination product is **24**. The solvent effects of the reaction of leuco



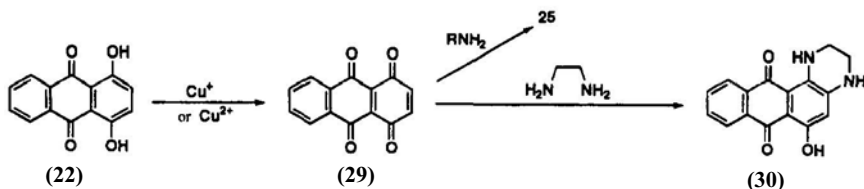
quinizarin (**9**) with butylamine have been studied in detail by Kikuchi and co-workers^{6,15} (Scheme 8). The same workers have also calculated thermodynamic parameters of this reaction.

Kikuchi *et al.* have observed that the initial attack of amine occurs at the carbonyl carbon, resulting in the formation of an ionic intermediate **26**. This reaction is very sensitive to the solvent polarity. Under nitrogen atmosphere, intermediate **27** is further aminated to give **28**. Oxidation of **27** and **28** gives **23** and **24**, respectively. Oxidation in nitrobenzene, however, results in dealkylation products. In the presence of air and triethylamine, decomposition of aminoanthraquinones occurs.

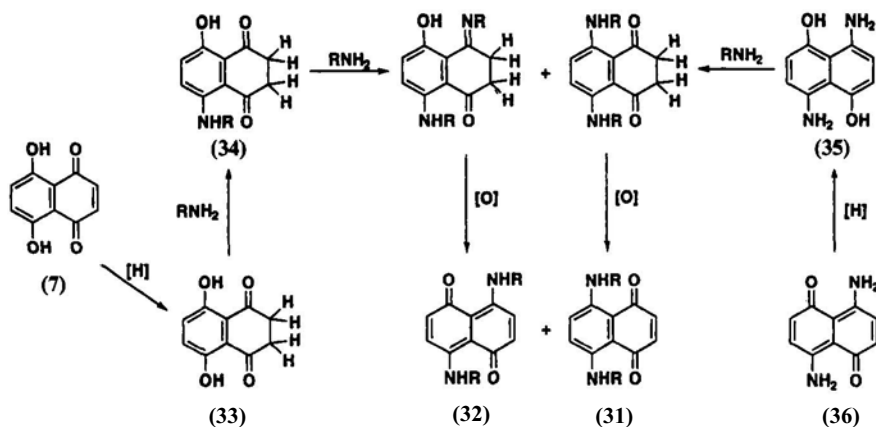
The alkylation of quinizarin (**22**) in the presence of copper salts has been studied by Matsuoka and co-workers.¹⁶ The reaction proceeds via oxidation by copper ion of **22** to quinizarinoquinone (**29**). 2-Alkylaminoquinizarin (**25**) was obtained in quantitative yield. The 1,2-ring-closure product (**30**) is obtained by the reaction of **22** with ethylenediamines in the presence of copper ions¹⁷ (Scheme 9).

By contrast, alkylation of naphthazarin (**7**) in the presence of sodium dithionite followed by oxidation gives 1,4-bis(alkylamino)-5,8-naphthoquinone (**31**).^{18,19} However, Kikuchi and co-workers²⁰ obtained isomeric 1,5-bis(alkylamino)-4,8-naphthoquinone (**32**) from the reaction of leuco naphthazarin (**33**) with alkylamine. They also isolated 5-alkylamino-leuco-naphthazarin (**34**) as an intermediate, which is further aminated at the 1-position to give **32**. Bloom and Dudek²¹ have studied the structure of leuco aminonaphthoquinones and their tautomeric equilibria in solution. They concluded that the reaction of leuco naphthazarin (**33**) or the leuco compound (**35**) derived from 1,5-diamino-4,8-naphthoquinone (**36**) with methylamine gives mixtures of 1,4-bis(methylamino)-**31** (R = Me) and 1,5-bis(methylamino)naphthoquinones **32** (R = Me) after oxidation of leuco aminonaphthoquinones (Scheme 10). Some of the structures of leuco aminonaphthoquinones are shown in Scheme 11.²⁰

Alkylation of naphthazarin copper complex (**37**)²² gives predominantly a mixture of 2(or 3),5-bis(alkylamino)-8-hydroxy-1,4-naphthoquinone (**38**) and 2,6-bis(alkylamino)-4,8-dihydroxy-1,5-naphthoquinone



Scheme 9



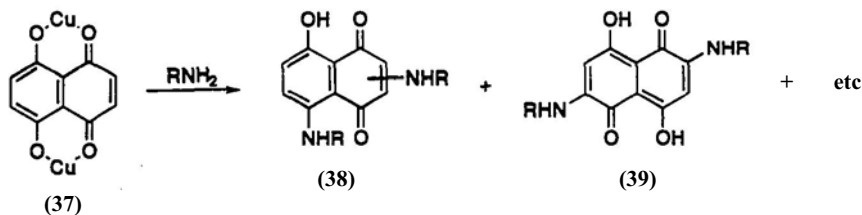
Scheme 10



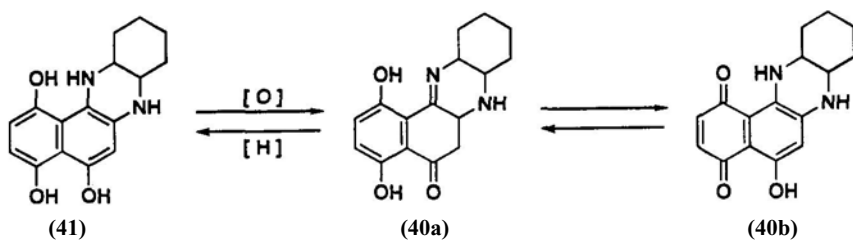
Scheme 11

(39), together with small amounts of 2-alkylamino-, and tris(alkylamino)-naphthazarin (Scheme 12). The structure of **39** has recently been assigned by NOESY NMR.²³

The redox behavior of aminonaphthoquinones has been investigated by Matsuoka and co-workers.¹¹ Reduction of quinoxaline quinone (**40**) by sodium dithionite in aqueous sodium hydroxide gives the corresponding leuco dye (**41**) which absorbs at 445nm. Compound **40** shows quinone-



Scheme 12



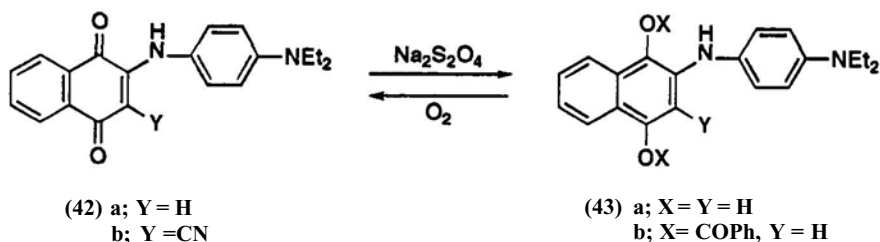
Scheme 13

quinoneimine tautomerism in chloroform solution and absorbs over the full range of the visible region. The leuco dye **(41)** can be isolated in a stable state and can be easily reoxidized to dye **40** by an oxidizing agent such as hydrogen peroxide. Dye **40** was regenerated as a mixture of two tautomers **(40a)** and **(40b)** (Scheme 13).

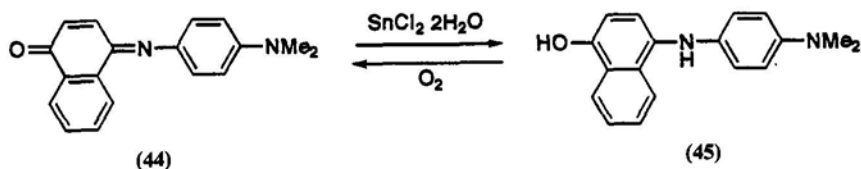
Reduction of 2-arylaminoanthraquinone dye **42a** (λ_{max} 560 nm) with sodium dithionite under a nitrogen atmosphere gives the leuco dye **43a**, which has an absorption maximum at 376 nm and is colorless. However, the leuco dye **43a** was immediately reoxidized to dye **42a** by atmospheric oxygen, although it could be isolated in a stable state as benzoyl ester **(43b)** (Scheme 14).¹¹

The leuco dye **45** can be obtained by the reduction of indonaphthol dye **44** (λ_{max} 455 and 630 nm) with tin(II) chloride in aqueous hydrochloric acid. The leuco dye **45** has maximum absorption at 300nm and is colorless. Isolation of **45** was unsuccessful owing to the rapid reoxidization of **45** to **44** by atmospheric oxygen (Scheme 15).¹¹ Stabilization of **45** was attained by acylation, etc. (Scheme 3).

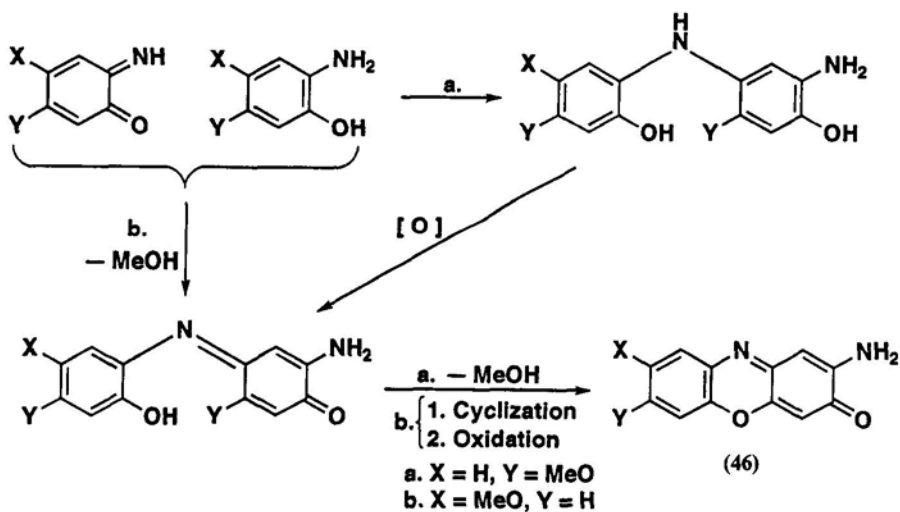
Polyhydroxybenzenes or aminophenol derivatives can be considered as leuco quinones or leuco quinoneimines. They are easily oxidized and couple



Scheme 14



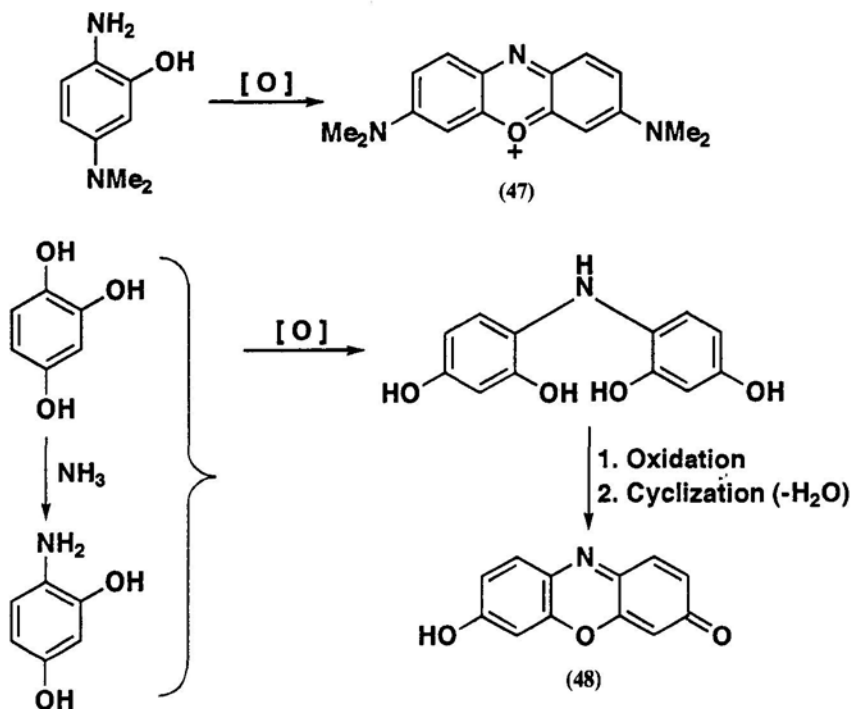
Scheme 15



Scheme 16

in the oxidized form to afford quinoneimine-type heterocyclic dyes such as phenoxazine or phenazine dyes. The autoxidation reaction of these leuco quinoid compounds has been used in hair dyes.²⁴ Autoxidation of 4- or 5-methoxy-2-aminophenols has been found to yield the corresponding 7- or 8-methoxy-2-aminophenoxazin-3-ones (**46**), which give orange-brown colors (Scheme 16).

The blue dye (**47**), formed from the autoxidation of 4-*N,N*-dimethylamino-2-hydroxyaniline, is the oxygen analogue of methylene blue. The autoxidation of 1,2,4-trihydroxybenzene, carried out in the presence of ammonia, gives the hydroxyphenoxazinone dye (**48**) via a 2,4-dihydroxyaniline intermediate (Scheme 17). Many types of phenoxazines, phenazines, and phenoxazinium salts can be obtained by autoxidation of polyhydroxybenzenes and their amino derivatives. Some autoxidative dyes may give poly-



Scheme 17

meric species as a result of carbon-carbon or carbon-nitrogen oxidative coupling.

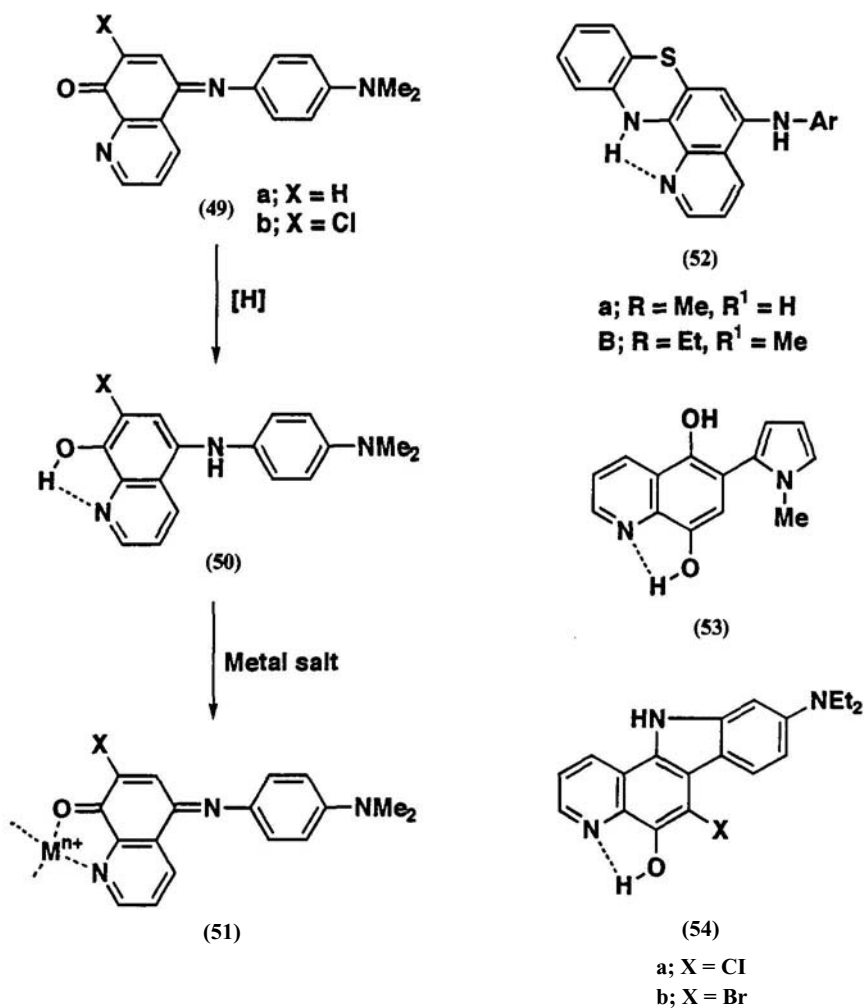
2.8. APPLICATION OF LEUCO QUINONES

Leuco naphthazarins have been well studied as hair dyes.²⁵ Human hair has been colored purplish red from dye solutions in aqueous benzyl alcohol. For example, **33** has been oxidized on hair during the drying process.

Although leuco quinones have been studied as color formers, their use in color-forming recording media has not been studied extensively due to their instability.

Recently, Yoshida and co-worker^{26 - 29} have developed a series of new color-forming systems using metal complexes of leuco quinones. Many bidentate ligands that produce a large bathochromic shift of absorption

maximum with an increase in molar extinction coefficient have been reported. The N,O-bidentate indoaniline-type ligand, 5-(4-dimethylamino-phenylimino)quinolin-8(5*H*)-one (**49a**)²⁶ readily forms complexes with metal ions to produce near-infrared absorption at around 720 nm. Hence, use of metal chelate complexation together with the redox process of the dye **49** is of particular interest for developing new near-IR color-forming systems. Reduction of **49a** with sodium dithionite in alkaline conditions

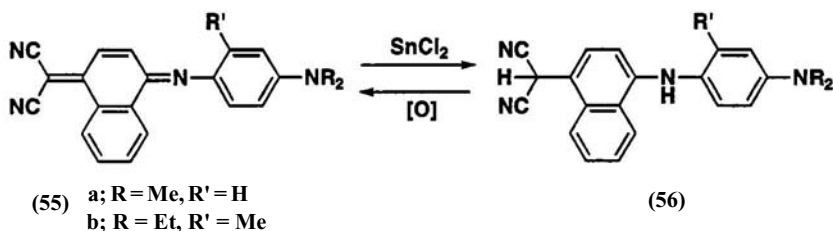


scheme 18

gives the leuco dye **50a** in high yield, which has weak absorption maximum at 403 nm. Leuco dye **50a** can be isolated as a stable compound. This may be attributed to the formation of an intramolecular hydrogen bond between the 1-nitrogen atom and 8-hydroxy group. Addition of copper salt to an ethanol solution of **50a** results immediately in the increase of absorbance at 724 nm suggesting oxidation to form the metal complex **51a**. Rapid formation of an intense absorption band in the near IR region is important from the viewpoint of some color-forming systems. Such color-forming systems can be applied to labels for use with diode laser readable direct thermal printing systems. It is also notable that the rate of color development and the absorption maximum of **51** can be affected by complexing metal salts. Related leuco quinoid dyes such as **52**,²⁷ **53**,²⁸ and **54**²⁹ have been reported which show similar color-developing behavior and formation of metal complexes (Scheme 18).

In the case of the naphthoquinone methine-type near-IR dye **55**, reduction with tin(II) chloride under acidic conditions gives the leuco dye **56**, which has weak absorption maxima at 350–359 nm in methanol. The leuco dye **56** can be isolated as a stable pale yellow compound. The oxidation behavior of **56** has been studied by adding benzoquinone as oxidant in methanol solution. Compound **56** immediately produced new absorption at 760 nm which is consistent with the absorption maximum of **55** (Scheme 19).³⁰ The absorption spectra of the leuco, quinone, and metal complex forms are summarized in Table 3.

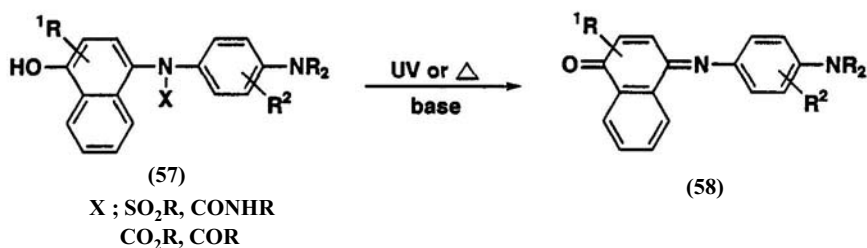
The leuco dye **57** (cf. dye **20**) has been used as a photosensitive¹² or a photothermographic material¹³ capable of producing a high-density cyan image. Dye **57** is stable enough not to be oxidized by oxygen of the air or by simple heating. Since the color developing reaction is activated by alkaline conditions, the photosensitive layer preferably contains bases such as amines or inorganic bases. Light- or heat-induced oxidation of the leuco dye **57** combined with cleavage of the N—X bond gave the indonaphthol-type cyan dye **58** (Scheme 20).



scheme 19

Table 3. Absorption Spectra of Quinone Derivatives²⁶⁻³⁰

	Leuco form		Quinone		Metal complex	
	rim	(ϵ)	nm	(ϵ)	nm	(metal ion)
50a	403	(2,800)	600	(16,600)	724	(Cu ^{II})
50b	403	(3,500)	635	(21,300)	745	(Fe ^{III})
52a	459	(3,700)	616	(10,800)	779	(Cu ^{II})
52b	454	(3,000)	654	(11,100)	834	(Cu ^{II})
53			484	(5,300)	598	(Cu ^{II})
54	353		435	(8,080),	ca.1000	(Fe ^{III})
			693	(5,530)		
56a	359	(11,100)	729	(25,500)		
56b	350	(11,000)	762	(30,800)		



Scheme 20

Some quinones, having the ability to form intra- and/or intermolecular hydrogen bonds, exhibit high molecular hyperpolarizability and are third-order nonlinear optical (NLO) materials. Compound **39** has a $\chi^{(3)}$ of 5×10^{-11} esu at 1.9 μm , and is a third-order NLO material.²³ The optoelectric properties of quinoid compounds correlate with their structures in crystals or on thin films.²³

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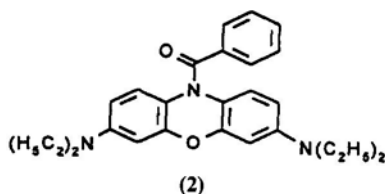
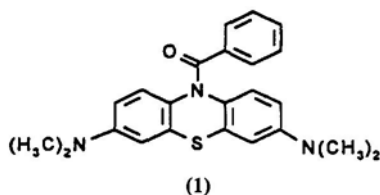
3

Thiazine, Oxazine, and Phenazine Leuco Dyes

TRAN VAN THIEN

3.1. INTRODUCTION

Benzoyl leuco Methylene Blue (1), which is a phenothiazine leuco dye, has been known since 1900. The material was developed to extend the range of hues and colors obtainable in such applications as pressure-sensitive carbonless paper and to complement other classes of leuco dyes such as triarylmethanes, crystal violet lactone, and fluorans. Benzoyl leuco Basic Blue 3 (2), which is a phenoxazine leuco dye, is a more recent development.



New applications have recently emerged, spurring the need for the development of new leuco dyes including leuco phenazine dyes: electrolytic

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Chemistry and Applications of Leuco Dyes, edited by Muthyala. Plenum Press, New York, 1997.

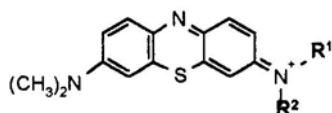
recording paper, transparencies for overhead projector, thermographic and photothermographic materials also known as Color Dry Silver.

3.2. THIAZINE LEUCO DYES AND APPLICATIONS

When Methylene Blue is reduced, the yellowish leuco cannot be isolated due to instant air oxidation. Benzoylation of the leuco form provides stabilization. There are also leuco thiazine dyes stable enough to be isolated without the need for arylation.

3.2.1. Acylated Leuco Thiazine Dyes

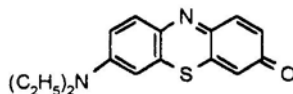
There are cationic thiazine dyes (3 to 5) and neutral thiazinone dyes exemplified by Methylene Violet (6). Like leuco Methylene Blue, leuco Methylene Violet is too air sensitive to be isolated and therefore requires acylation.



(3) AzureA $R^1-R^2=H$

(4) AzureB $R^1=H; R^2=CH^3$

(5) Methylene Blue $R^1=R^2=CH^3$



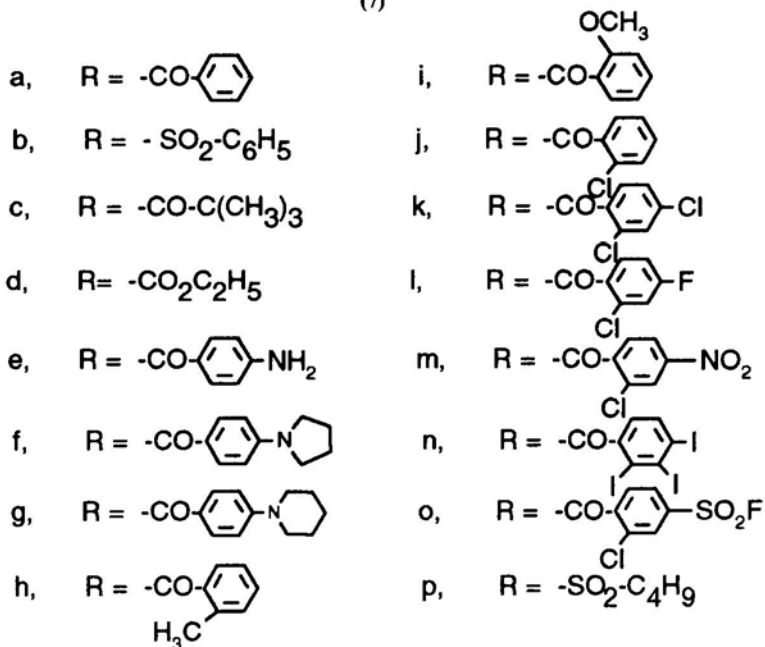
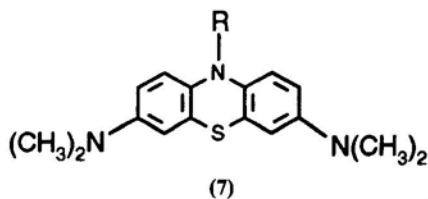
(6)

Methylene Violet

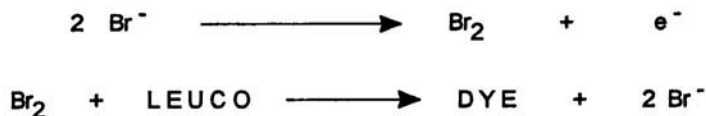
3.2.1.1. Acylated Leuco Cationic Thiazine Dyes

The leucos **7a-d** are described as useful in printing ink for preventing forgery,¹ whereas **7e-g** are used in pressure sensitive copying paper.²

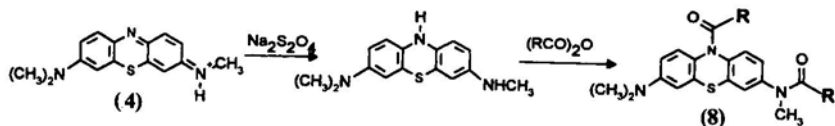
The leucos **7h-o** are claimed in electrolytic recording paper using a process coined “electrochromic recording” which is an irreversible electrooxidation of the leuco dye to regenerate Methylene Blue, not to be confused with reversible electrochromic display. The process consists of passing an electrical pulse through a substrate containing the leuco dye and



ammonium bromide to generate bromine *in-situ* which acts as an oxidizing agent for leuco Methylene Blue.³ The leuco **7p** is claimed as a sublimable leuco dye in thermal dye transfer imaging wherein it is converted to Methylene Blue on the receptor sheet by an incorporated oxidizer.⁴

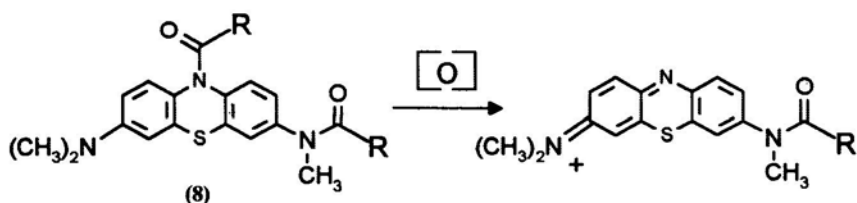


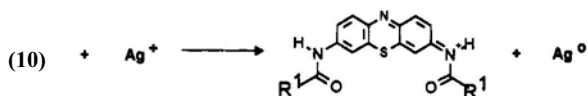
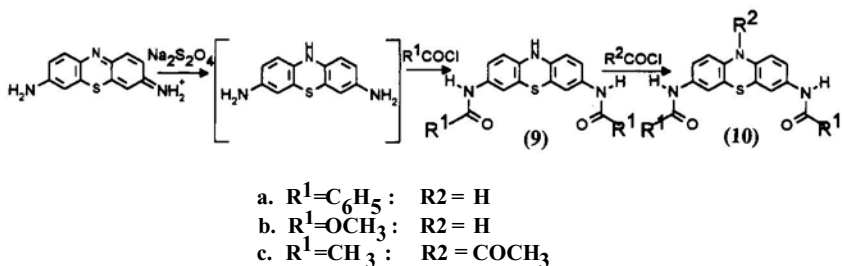
Instead of using Methylene Blue, Azure B is reduced and acylated.⁴ The resulting leucos **8a-t** are also described as useful in electrolytic recording.⁵



- | | |
|--|--------|
| a, R = CH ₃ | k, R = |
| b, R = CH ₂ (CH ₃) ₂ | l, R = |
| c, R = | m, R = |
| d, R = CH ₂ -O-CH ₃ | n, R = |
| e, R = | o, R = |
| f, R = C ₅ H ₁₁ | p, R = |
| g, R = CCl ₃ | q, R = |
| h, R = CH ₂ -O- | r, R = |
| i, R = | s, R = |
| j, R = | t, R = |

In contrast to leuco Methylene Blue, acylated leuco Azure B fails to regenerate the original dye by virtue of the fact that the exocyclic amino group was also acylated during the leuco dye synthesis and the amide group remains on oxidation. Acylated Azure **B** is formed instead resulting in a different color. The leucos **8a-t** are reported to give green black or blue black images.



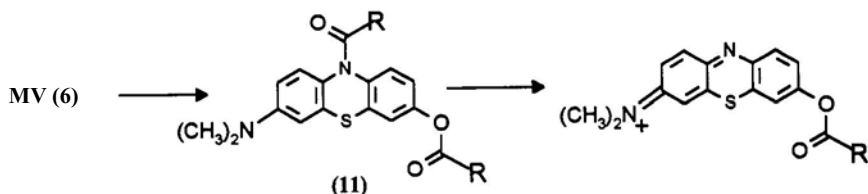


Safranin O is reduced to a leuco intermediate and acylated in one step to produce the leuco **9**. Only the exocyclic amino groups are acylated at this point due to their higher reactivity. The ring amino groups can then be acylated with another acid chloride to produce the safranin leucos **10a-c** which are claimed to give pink or purple images in Color Dry Silver. In this application, light-sensitive silver halide is the oxidizing species.⁶

3.2.1.2. Acylated Leuco Thiazinone Dyes

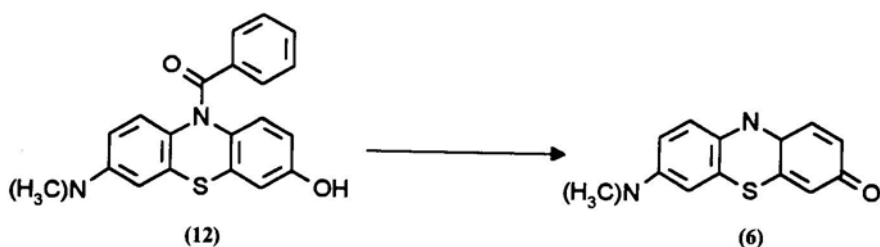
The leucos **11a-d** are claimed to give blue gray images in electrolytic recording instead of the purple color of Methylene Violet from which they are derived.⁷

As in the case of the leucos Azure A and B, the exocyclic acyl group is not eliminated on oxidation, resulting in a Methylene Blue-type cationic



- a, $R = CH_3$;
 b, $R = C_6H_5$;

- c, $R = C_3H_7$
 d, $R = C_6H_4-O-CH_3$

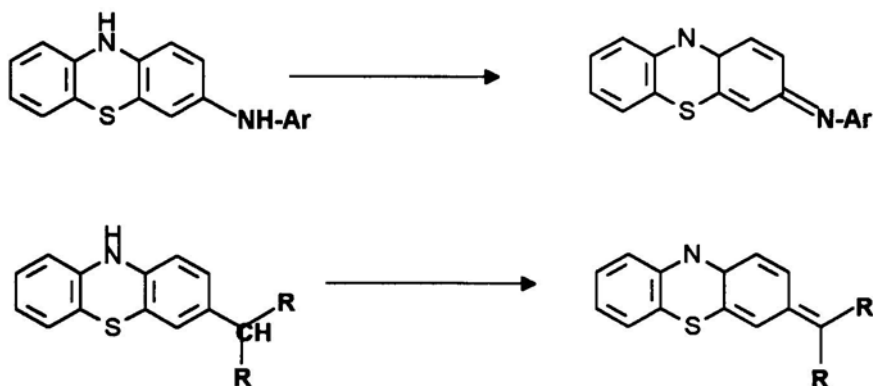


dye. The color obtained is rather muddy but this can be seen as desirable since a black leuco dye is much sought after.

Compound **12** can be described as a true leuco Methylene Violet since a purple image is obtained on oxidation with a metal nitrate.^{8a}

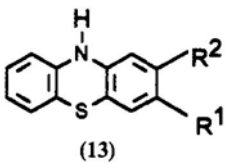
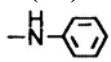
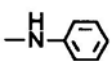
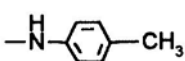
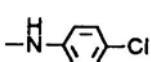
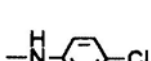
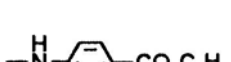
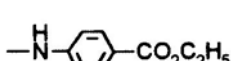
3.2.2. Nonacylated Leuco Thiazine Dyes

These leuco dyes are stable enough to be isolated without the need for acylation. Some are more resistant than others to air oxidation depending on their redox potential.⁹

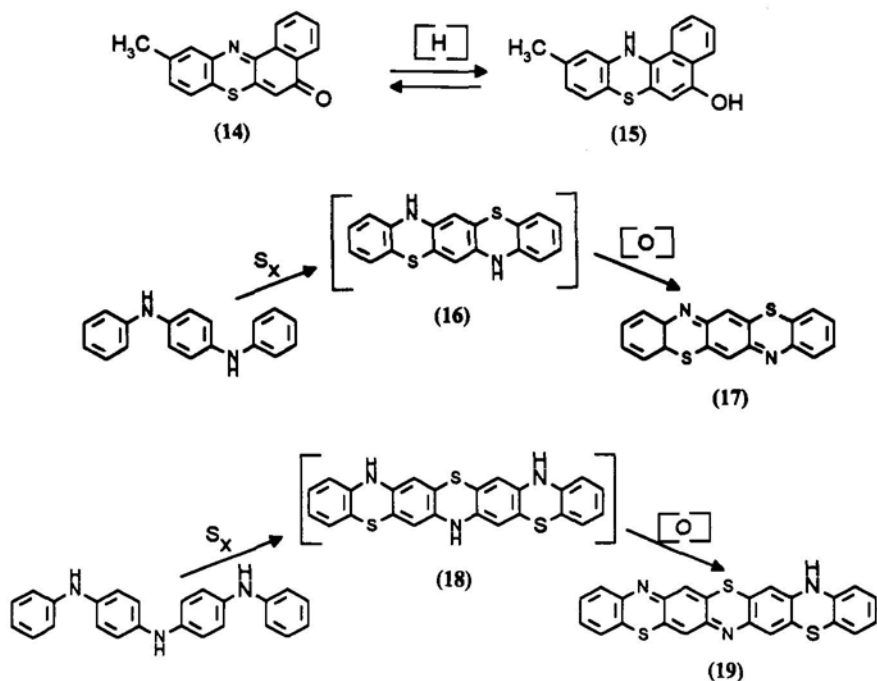


As shown in Table 1, the introduction of an electron-withdrawing group raises the redox potential and stabilizes the leuco against air oxidation. In one extreme case, this stabilization has become so efficient that leuco **13o** is too stable to be oxidized back to the dye, thus severely limiting its usefulness as an imaging material.

Table 1. Effect of Substituents on the Redox Potential and Reactivity of Thiazine Leuco Dyes

 (13)			
	R ¹	R ²	E _{ox}
a	CH(CO—C ₆ H ₅) ₂	H	—
b	CH(CN) ₂	H	—
c	CH(CN) ₂	SO ₂ C ₆ H ₅	+0.70 V
d	CH(CN)CO ₂ C ₂ H ₅	H	—
e	CH(CN)CO ₂ C ₂ H ₅	SO ₂ C ₆ H ₅	+0.65 V
f	CH(CN)CONH ₂	H	+0.54 V
g	CH(CN)CONH ₂	SO ₂ C ₆ H ₅	+0.69 V
h	CH(CN)CO—C ₆ H ₅	H	—
i		H	+ 0.25V
j		SO ₂ C ₆ H ₅	+ 0.29V
k		SO ₂ C ₆ H ₅	+0.31V
l		H	+0.25V
m		SO ₂ C ₆ H ₅	+0.35V
n		H	+0.35V
o		SO ₂ C ₆ H ₅	>+1.0V

Benzo[1,2-*a*]-8-methyl-9-azaphenothiazinone (**14**) was reduced to a leuco form **15** which was too unstable to be isolable.¹⁰ The leucos **16** and **18** obtained from thionation of *N,N*-diphenyl-*p*-phenylenediamine and *p,p'*-dianilinodiphenylamine, respectively, are also air sensitive.¹¹ They are oxidized to thiazine dyes **17** and **19** which are reported to absorb in the near infrared.

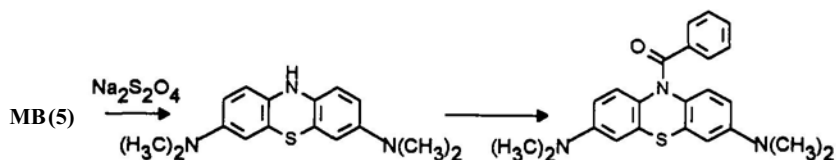


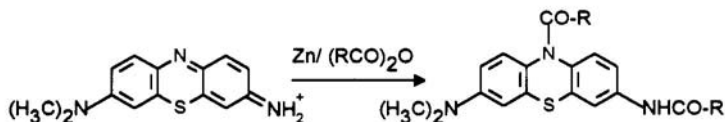
3.2.3. Synthetic Methods

3.2.3.1. Acylated Leuco Thiazine Dyes

The standard procedure for the synthesis of leuco dyes related to benzoyl leuco Methylene Blue is straightforward. The one-pot synthesis is carried out in a two-phase water-toluene system. Methylene Blue is first dissolved in the aqueous phase and reduced with sodium dithionite under nitrogen and with stirring. The yellowish leuco is extracted into the organic phase where it is allowed to react with an acid chloride, the aqueous phase being made alkaline.

Leuco Azure A or B is obtained by refluxing the dye in an acid anhydride in the presence of zinc powder wherein the dye is reduced and acylated at the same time.





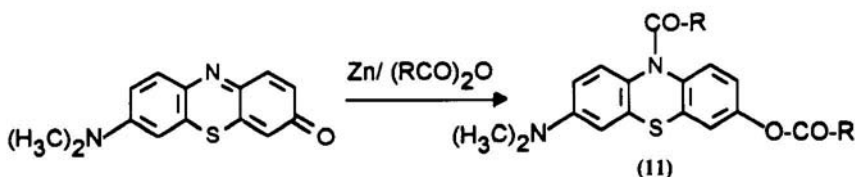
Synthetic Method 1: 6-(dimethylamino)-3-(N-acetyl-N-methylamino)-10-acetylphenothiazine 8a (procedure from US. Patent 4,652,643).⁵ A mixture of 9.0g of 6-(dimethylamino)-3-(methylamino)phenothiazine-5-ium chloride (Azure B), 150.0ml of acetic anhydride, and 10.0g of zinc dust was maintained at reflux temperature for approximately 4 hs. After the reaction mixture was cooled to ambient temperature, it was poured into ice water with stirring and 300ml of toluene was added. After stirring for approximately 30 min the toluene layer was separated and washed twice, once with tap water and once with saturated aqueous sodium chloride solution. The toluene was then distilled off at reduced pressure. The residue which remained was dissolved in ethyl acetate and separated into various components by subjecting the solution to column chromatography using silica gel as substrate. Elution with ethyl acetate yielded a white-colored solid.

Synthetic Method 2: 6-(dimethylamino)-3-[N-(4-methylphenylcarbonyl)-N-methylamino]-10-(4-methylphenylcarbonyl)-phenothiazine (8m) (procedure from U. S. Patent 4,652,643).⁵ The reaction vessel was purged of residual air with nitrogen and, while maintaining a nitrogen atmosphere, there was placed in the vessel 10.0g of Azure B, 500.0ml of water, and 500.0ml of toluene. With stirring, there was added to the resulting mixture 10.0g of sodium carbonate and 15.0g of sodium dithionite. The resulting mixture was stirred for approximately 15 min at ambient temperature and the water layer was separated and discarded. To the toluene layer, 10.0g of sodium dithionite was added and the resulting mixture was heated at reflux temperature until all of the water was azeotroped off. After the mixture had dried, it was cooled to approximately 70°C and 15.0g of disodium phosphate was added. To this mixture, there was added a solution of 20ml of 4-methylbenzoyl chloride dissolved in 30.0 ml of toluene. The reaction mixture was heated at reflux temperature for approximately 2½ h. After cooling the resulting mixture to ambient temperature, 500ml of water and 15.0g of disodium phosphate were added. This mixture was then refluxed for approximately 30 min and then cooled to room temperature. The toluene layer was separated and saved and the water layer discarded. The toluene layer was washed twice, each time with 400ml of water, once with 400ml of aqueous saturated sodium carbonate solution, then with 400 ml of water and finally with 400ml of aqueous saturated sodium chloride solution. All of the aqueous washes were discarded. The toluene layer was then

evaporated to dryness under reduced pressure. The residue was slurried in a mixture of 200ml of isopropyl alcohol, 100ml of water, and 20.0g of disodium phosphate at approximately 80°C for 10 min. After cooling, the solid was collected by filtration and dried to obtain 8.24 g of a white powder which melted at 220 to 224°C.

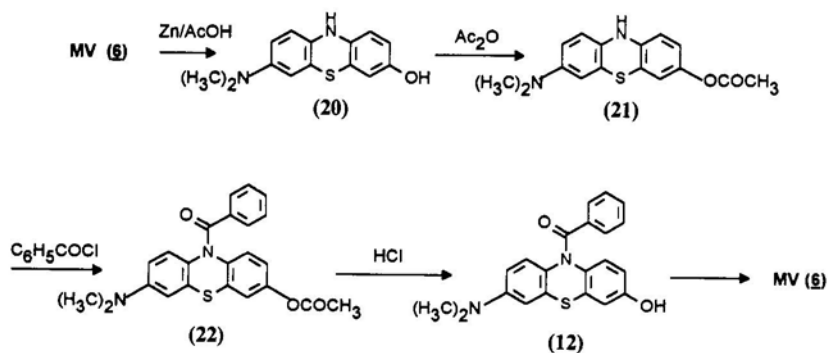
3.2.3.2. Acylated Leuco Thiazinone Dyes

Methylene Violet, which is a well-known phenothiazinone dye, is also reduced and acylated in one step by refluxing with zinc powder in an acid anhydride.



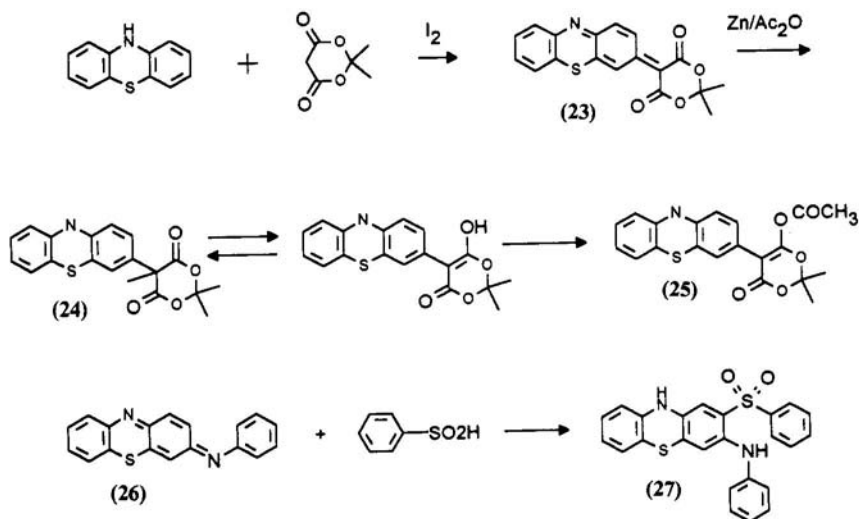
Synthetic Method 3: 6-dimethylamino-3-acetoxy-10-acetylphenothiazine (11a) (procedure from US. Patent 4,604,458).⁷ Under a nitrogen atmosphere, a mixture of 5.0 g of 7-dimethylaminophenothiazin-3-one (Methylene Violet), 75.0ml of acetic anhydride, 5.0ml of pyridine, and 50g of zinc dust was maintained at reflux temperature for approximately 3 h. After cooling to room temperature, the reaction mixture was filtered to remove the insoluble materials and the filter cake was washed twice, each time with 50.0ml of acetone. The combined filtrate and acetone washes were concentrated and poured slowly into water and 100ml of toluene was added to the resulting mixture. After stirring for approximately 30 min, the layers were separated and the aqueous layer was discarded. The organic extract was treated with activated charcoal, filtered, and the toluene was evaporated off at reduced pressure to obtain a gummy residue. The residue was dissolved in ethylacetate and the resulting solution was passed through a chromatographic column packed with silica gel. Elution with ethylacetate yielded a solid as a white powder (2.6g) which melted at 124 to 128°C.

Reduction of Methylene Violet with zinc in acetic acid gives the air-sensitive leuco **20** which is further reacted with acetic anhydride in mild conditions to yield the acetylated leuco **21**. The latter being air stable can be isolated and, the ring N-H being less reactive is not affected by acetylation at room temperature. The leuco **21** is again aroylated to produce the leuco **22**. Selective hydrolysis provides the desired leuco dye **12** which regenerates the true Methylene Violet (**6**) on oxidation.^{8a}



3.2.3.3. Nonacylated Leuco Thiazine Dyes

The thiazine dyes used in the preparation of this type of leuco are obtained through oxidative coupling of phenothiazine with an active methylene compound or an aniline. The reduction of the dye **23** with zinc powder in acetic acid is straightforward.⁹ Treatment of the leuco **24** with acetic anhydride at 40°C yields a more air stable leuco **25**.⁹ Addition of arylsulfonic acid to thiazine dyes such as **26** produces directly leuco dyes such as **27**.^{8b}



Synthetic Method 4: 3-(4-carbethoxyanilino)-phenothiazine (13n) (procedure from U.S. Patent 4,710,570).^{8b} To a warm and stirred suspension of 4.0g (0.02 mol) of finely powdered phenothian zine and 4.0g (0.024 mol) of ethyl-p-aminobenzoate in 200ml of methanol was added a solution of 10.0g of iodine in 150ml of methanol. After stirring at room temperature for 2 h, the dark precipitate was filtered, washed repeatedly with methanol, and dissolved in 100ml of chloroform and 10ml of triethylamine. The chloroform solution was shaken with water and separated. The aqueous layer was discarded and the organic layer evaporated. The residue was purified through alumina. Recrystallization from ether gave 5.5 g (76%) of the dye 3-(4-carbethoxyphenylimino)-3H-phenothiazine as purple leaflets.

To a stirred suspension of 1.0g of the above dye in some 50ml of warm acetone was added excess zinc dust and a few drops of concentrated hydrochloric acid. The mixture was stirred until the coloration discharged, and then filtered. The cake was extracted with hot acetone. The filtrate and extracts were combined, concentrated, and poured into water. The precipitate was filtered, washed repeatedly with water and cold methanol, and dried. Recrystallization from methanol gave 0.9g (90%) of the leuco dye 3-(4-carbethoxyanilino)phenothiazine as a white powder which gradually turned pinkish on contact with air.

Synthetic Method 5: 2-benzenesulfonyl-3-(p-carbethoxyanilino)phenothiazine (13o) (procedure from U.S. Patent 4,710,570).^{8b} To a warm, stirred solution of 1.8 g of dye 3-(4-carbethoxyphenylimino)-3H-phenothiazine in 50 ml of tetrahydrofuran was added 0.8 g of benzenesulfinic acid (obtained by adding dilute hydrochloric acid to an aqueous solution of benzenesulfinic acid sodium salt to cause precipitation of the free acid). After stirring 1 h at 40°C the solvent was evaporated off under reduced pressure. The yellowish solution was poured into water. The precipitate was filtered, washed repeatedly with distilled water and methanol. Recrystallization from methanol gave 1.9 g (76%) of the leuco dye 2-benzenesulfonyl-3-(4-carbethoxyanilino)phenothiazine (13o) as a yellowish powder.

3.3. OXAZINE LEUCO DYES AND APPLICATIONS

3.3.1. Acylated Oxazine Leuco Dyes

Benzoyl leuco Basic Blue 3 (2) is a typical cyan leuco oxazine used in carbonless copy paper. To satisfy the requirements of new applications such as electrolytic recording and Color Dry Silver, new oxazine leucos have been

developed that can offer colors other than cyan such as red, purple, and blue violet.

The introduction of electron-withdrawing groups on the exocyclic amino groups of the oxazine dyes is one method employed to create a hypsochromic shift and obtain colors ranging from orange to violet.⁶ The redox potential of the new dyes is probably raised owing to the presence of the electron-withdrawing groups which leads to the nonacylated leuco oxazine dyes being stable enough to be isolated, as shown in Table 2.

The reductive acetylation of Brilliant Cresyl Blue (29) yields 1,9-dimethyl-4-acetamido-8-diethylaminoimidazophenoxazine (30) which gives a purple image in electrolytic recording.¹² Other similar oxazine leucos (31–34) have also been developed for electrolytic recording.¹³ The leucos 33 and 34 produce blue violet images.

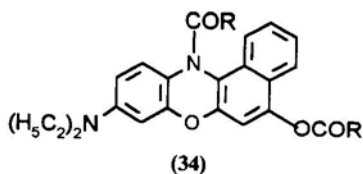
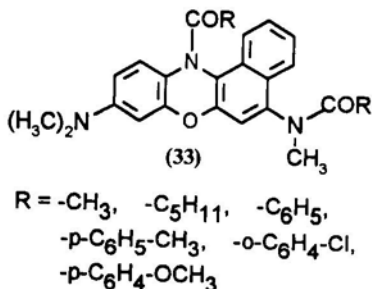
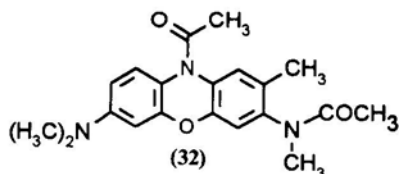
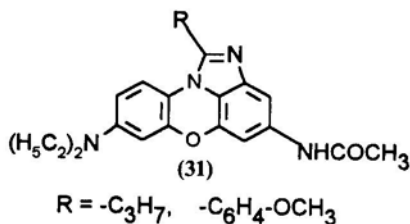
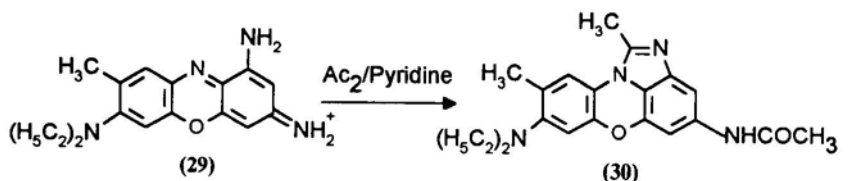
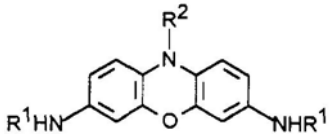
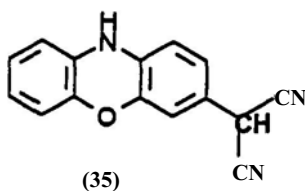


Table 2. Effect of Substituents on the Color of Oxazine Dyes

 (28)			
	R ¹	R ²	Dye color
a	COCF ₃	H	Purple
b	SO ₂ CH ₃	H	Orange
c	COCF ₃	CONHC ₄ H ₉	Purple
d	COC1 ₃	CONHC ₄ H ₉	Magenta
e	COCHC1 ₂	CONHC ₄ H ₉	Red
f	CH ₂ CF ₃	COCF ₃	Blue (595 nm)
g	H	COC ₆ H ₅	Green
h	CO ₂ C ₂ H ₅	COC ₆ H ₅	Red
i	CO ₂ C ₂ H ₅	CONHC ₄ H ₉	Purple

3.3.2. Nonacylated Oxazine Leuco Dyes

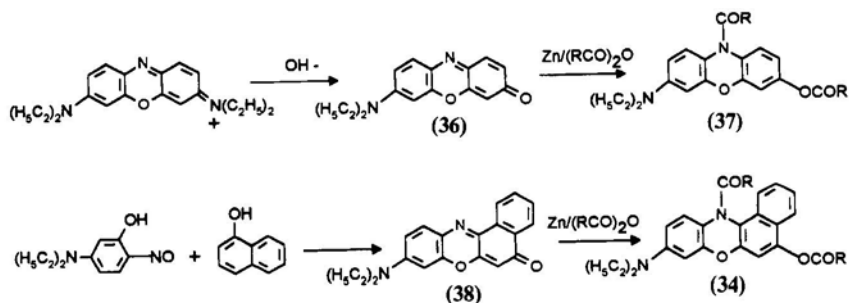
Examples of nonacylated oxazine leucos are rare, possibly due to the high cost of the phenoxazine starting material. Apart from a few examples described earlier, the leuco **35** is reported to give a blue image.⁸



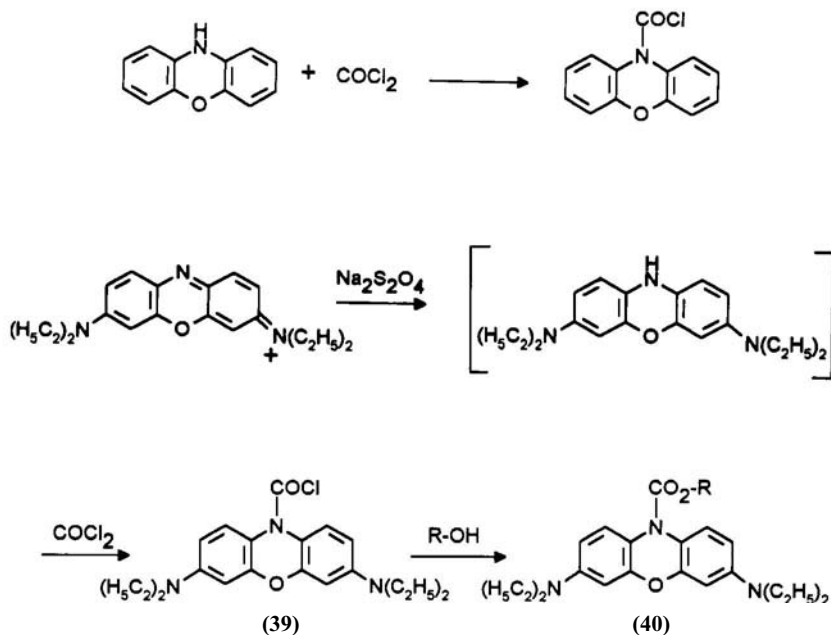
3.3.3. Synthetic Methods

The availability of oxazine leucos is dictated by the ease of synthesis of the oxazine dyes.

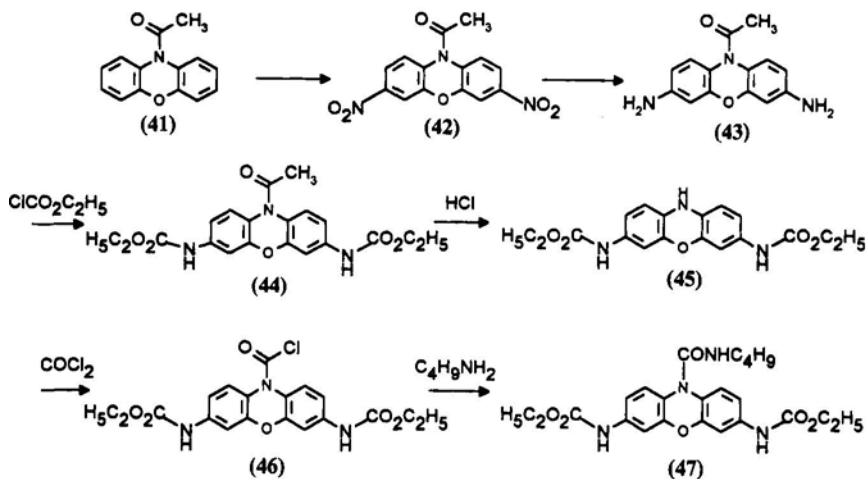
The purple phenoxazone **36** is obtained by alkaline hydrolysis of Basic Blue 3.14 The benzophenoxazone **38** is obtained by coupling of 2-nitroso-5-diethylaminophenol with α -naphthol.¹⁴ The leucos **37** and **34** are obtained by refluxing the corresponding dyes with zinc powder in acid anhydride.



Based on the well-known reaction of phenoxazine with phosgene,¹⁵ leuco Basic Blue 3 was treated with phosgene to form the stable 10-chlorocarbonyl-3,7-diethylaminophenoxazine (39) which can be isolated and further reacted with alcohol or amine.¹⁶



Starting from phenoxazine, the leuco 47 is obtained through a multistep reaction involving nitration, reduction, and acylation.⁶



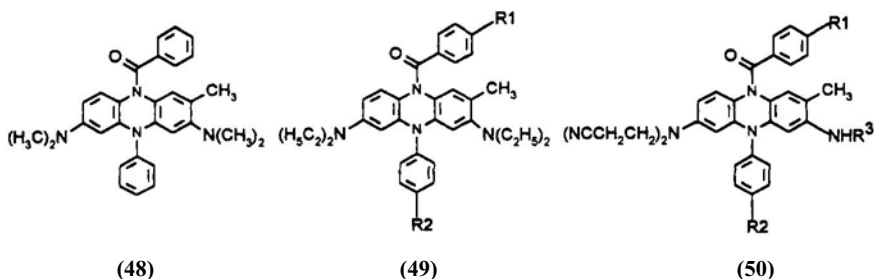
Synthetic Method 6: 9-diethylamino-5-(N-acetyl-N-benzylamino)-12-acetylbenzo[a]phenoxazine (**33**) (procedure from U. S. Patent 4,604,461).¹² A mixture of 14.0 g of 9-diethylamino-5-(N-benzylamino)benzophenoxazin-7-ium chloride, 75.0 ml of acetic anhydride, 5.0 ml of pyridine, and 7.0 g of zinc dust was maintained at reflux temperature for approximately 2 h. After cooling to room temperature, the reaction mixture was filtered to remove the insoluble material and the filter cake was washed twice, each time with 50 ml of acetone. The filtrate and the washes were combined, concentrated, and slowly poured into a stirred mixture of water and toluene. After stirring the mixture for 30 min, the organic layer was separated, treated with decolorizing charcoal, filtered, and the resulting clarified toluene solution was evaporated under reduced pressure to afford 15.17 g of 9-diethylamino-5-(N-acetyl-N-benzylamino)-12-acetylbenzo[a]phenoxazine as a pale brown powder which melted over the range of 86 to 91°C.

Synthetic Method 7 : 1,9-dimethyl-4-acetarnido-8-diethylaminoimidazo-phenoxazine (**31**) (procedure from U.S. Patent 4,604,462).¹² A mixture of 10 g of 1,3-diamino-7-diethylamino-8-methylphenoxazin-5-ium chloride (Brilliant Cresyl Blue), 50 ml of acetic anhydride, 10 g of zinc dust, and 10 ml of pyridine was maintained at 85 to 90°C for approximately 1 h. After cooling to room temperature, the reaction mixture was poured into a mixture of water and toluene and the resulting aqueous layer was discarded. The toluene solution was washed twice, first with water and then with

saturated sodium chloride solution. The toluene was removed by evaporation at reduced pressure. The residue was recrystallized from isopropanol and the solid obtained was recrystallized from ethanol to obtain 0.2g of 1,9-dimethyl-4-acetamido-8-diethylaminoimidazophenoxazine as a white solid which melted at 217 to 218°C.

3.4. PHENAZINE LEUCO DYES AND APPLICATIONS

Phenazine leuco dyes, like their thiazine and oxazine analogues, have also found application in electrolytic recording, overhead transparencies, and Color Dry Silver. The phenazine leuco **48** is employed in electrolytic recording,¹⁷ whereas compounds **49**, **50** are described as useful in thermographic and photothermographic systems.¹⁸



$R^1 = \text{H, Cl, Br, F, CF}_3, \text{CN, SO}_2\text{CH}_3, \text{SO}_2\text{C}_6\text{H}_5$

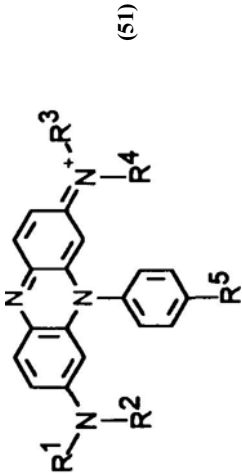
$R^2 = \text{H, CH}_3, \text{OCH}_3$

$R^3 = \text{CH}_2\text{Cl, CHCl}_2, \text{C}_6\text{H}_5, \text{C}_6\text{H}_4\text{-CF}_3, \text{C}_6\text{H}_4\text{-SO}_2\text{-C}_6\text{H}_5$

Phenazine leucos are generally more reactive and more susceptible to air oxidation than the thiazines and oxazines. Incorporation of electron-withdrawing groups on the acyl substituent at the 10-position of the leuco dye can provide a substantial improvement in the thermal and light stability of the leuco form and it is found that in general the stronger the electron-withdrawing character of the acyl substituents the more stable the leuco is.¹⁸

Phenazine leucos are capable of providing yellow, orange, red, and magenta images whereas thiazine and oxazine leucos are normally restricted to turquoise, blue, and purple colors.¹⁹ Color depends on the electronic nature of substituents R^1 to R^4 , as shown in Table 3.

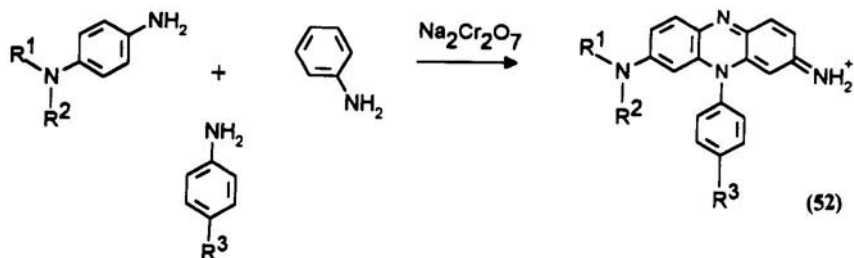
Table 3. Effect of Substituents on the Color of Phenazine Dyes

 (51)						
R ¹	R ²	R ³	R ⁴	R ⁵	λ _{max}	
a	CH3	CH3	CH3	CH3	571nm	
b	CH3	CH3	CH3	NO2	564nm	
c	CH3	CH3	CH2CO2H	OCH3	547nm	
d	C2H5	C2H5	C2H5	OCH3	573nm	
e	C2H5	C2H5	H	OCH3	555nm	
f	CH2CH2CN	CH3	CH3	OCH3	560nm	
g	CH2CH2CN	CH2CH2CN	CH3	OCH3	560nm	
h	CH2CH2CN	CH2CH2CN	H	OCH3	533nm	
i	CH2CH2CN	CH2CH2CN	CO—C6H5—CF3	OCH3	454, 523nm	
j	CH2CH2CN	CH2CH2CN	CH2CO2H	OCH3	544nm	
k	CH2CH2CN	CH2CF3	CO—C6H5Cl2	H	514nm	

Phenazine leucos until now are usually substituted at their 3 and 6 positions by amino groups due to the normal method of synthesis of the parent phenazine dyes. These types of leuco dyes are reactive. An alternative method of dye synthesis allows access to phenazine dyes with just one substituent at the 3-position.²⁰ The resulting leuco dyes are called half diazine leucos. The loss of one exocyclic amino group leads to higher redox potential and results in less reactive leuco dyes, more useful in applications such as thermographic and photothermographic imaging, particularly Color Dry Silver.

Synthetic Methods

The new phenazine dyes are prepared according to established procedures with some modifications:

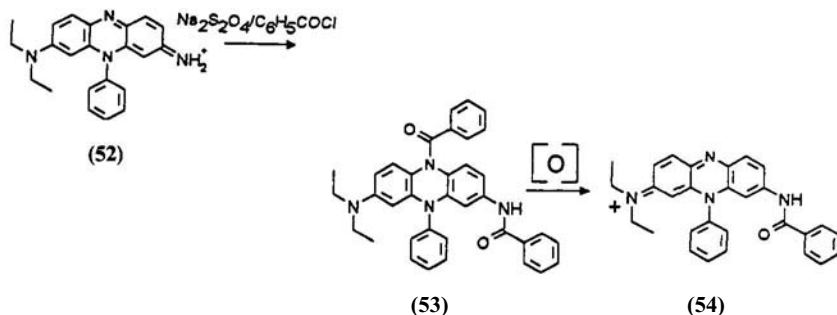


Synthetic Method 8: 9,10-dihydro-9-phenyl-10-(4-phenylsulfonylbenzoyl)-3,6-di(N, N-diethylamino)phenazine (procedure from U. S. Patent 4,889,932).¹⁸ Into a 1-liter, three-necked round-bottom flask equipped with a mechanical stirrer, pH electrode, and an argon inlet and outlet, was added 10 g (0.023 mol) of tetraethylphenosafranine and 200 ml of deionized water. The mixture was stirred for several minutes to dissolve the dye as completely as possible. Methylene chloride (40 ml) was then added, and the system was flushed with argon. The pH was adjusted to 10 with 20% aqueous NaOH, and 8 g (0.046 mol) of sodium dithionite was added all at once as a solid. The pH dropped to between 3 and 4 and the solution turned from purple to olive-green over several minutes. The solution was stirred for about 20 min. The acid chloride, 9.69 g (0.035 mol) of p-phenylsulfonylbenzoylchloride, ground to a fine powder and suspended in 60 ml of methylene chloride, was added dropwise over a period of 30–45 min., the pH being adjusted continuously with NaOH solution to keep it between 3 and 4.5.

After the addition of acid chloride, about 25 ml of methylene chloride was used to rinse the residual acid chloride into the flask. The mixture was stirred for about 3 h. The pH was then adjusted to between 9.5 and 10 and the solution was stirred for an additional hour. The organic layer was separated from the aqueous layer and washed once with 5% NaOH solution. The solution was dried over calcium sulfate and the methylene chloride was evaporated leaving about 10.36 g (69%) of crude product. Decolorizing three times with Attapulugus clay yielded a light yellow brown methylene chloride solution which, on removal of solvent, gave about 5.2 g of product (35%).

Synthetic Method 9: N-[8-bis(2-cyanoethyl)-9-[4-(phenylsulfonyl)-benzoyl]-9,10-dihydro-10-phenyl-2-phenaziny]-4-phenylsulfonylbenzamide (53) (procedure from US. Patent 4,889,932).¹⁸ A 3-liter round-bottom flask fitted with a mechanical stirrer was loaded with 16.6 g (0.066 mol) of 4-[di(2-cyanoethyl)amino]aniline in 800 ml of deionized water. A 10% excess of aniline (13.56 g, 0.1456 mol) and 100ml of deionized water were added to the mixture. The mixture was cooled to 0°C in an ice bath, and 10 ml of concentrated hydrochloric acid in 25 ml of water was added. Then 6.31 g (0.083 mol) of sodium dichromate in 25 ml of water was added. The temperature rose to 7°C. Stirring was continued as 9ml of concentrated hydrochloric acid in 25 ml of distilled water was added over a period of 2 h. After 16 h the temperature had risen to 20°C. The mixture was heated under reflux for 4 h and then filtered hot. The filter cake was washed with 1.5 liters of boiling water. The combined filtrates were concentrated to 1.4liters by vacuum evaporation, and then heated to 75°C as 200g of sodium chloride was added. The mixture was cooled to room temperature, chilled in an ice bath, and the solid was then recovered by filtration to give 14.6g (yield = 51.6%), $\lambda_{\max} = 537\text{nm}$ in methanol.

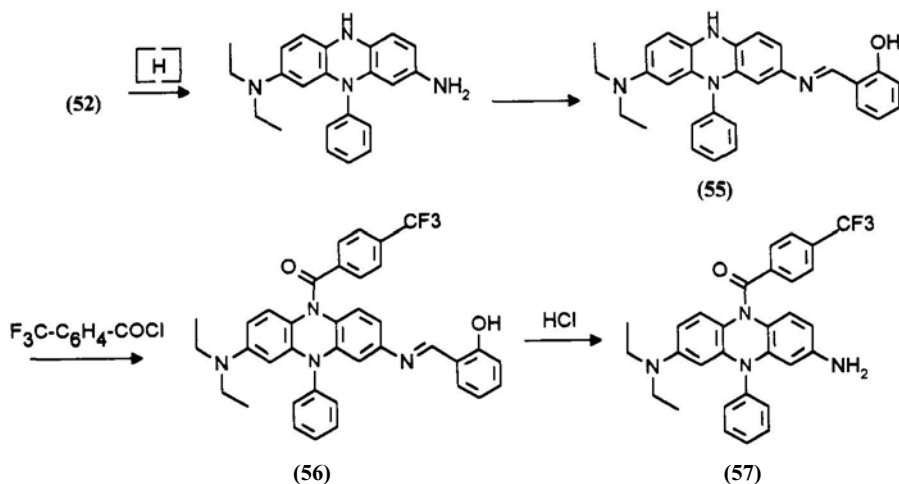
A 1-liter three-necked flask was fitted with a Claisen head equipped with two dropping funnels, a mechanical stirrer, and a pH electrode. A solution containing 5g (0.012 mol) of the dye prepared above, 210 ml of water, and 0.2 g of ethylenediaminetetraacetic acid was added to the flask and stirred, while 250 ml of methylene chloride was added. The system was closed and flushed with argon, the pH was adjusted to 10, then 2.44 g (0.014 mol) of sodium dithionite was added. The solution turned orange and the pH dropped to 3.7. Aqueous 25% NaOH solution was added to bring the pH to 4.5, and then 7.53 g (0.027 mol) of 4-phenylsulfonylbenzoylchloride in 60 ml of methylene chloride was added dropwise. After 1½ h the pH was raised to 10–11. The methylene chloride layer was separated and dried over



calcium sulfate. The solution was treated with about 10 g of Attapulugus clay and filtered. The solvent was then evaporated, leaving 8.14 g of solid (79%).

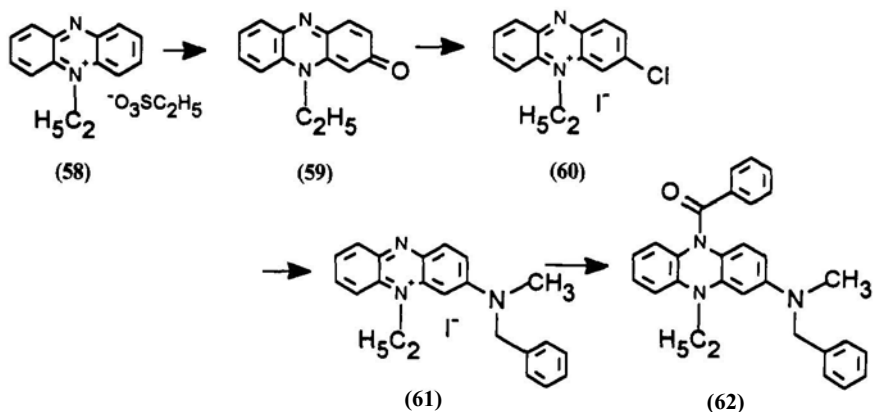
As in the case of thiazine and oxazine leuco dyes described earlier, the reductive acylation of the phenazine dye **52** results in the acylation of the exocyclic amino group.¹⁸ The phenazine leuco obtained **53** retains the exocyclic amide group on oxidation resulting in the acylated phenazine dye **54**, the color of which is different from the one intended.

An alternative method has been described in which the exocyclic free amino group of the leuco dye is protected with salicylaldehyde.²⁰ The resulting leuco **55** is acylated at its 10-position **56** and the salicylalimine protecting group is hydrolyzed with hydrogen chloride leaving a phenazine leuco dye possessing an exocyclic free amino group **57**. This leuco dye regenerates the original phenazine dye **52** on oxidation.



Synthetic Method 10: 3-amino-4-diethylamino-9-phenyl-10-(2-trifluoromethylbenzoyl)-9,10-dihydrophenazine (57) (procedure from Japanese Patent 63-112569).²⁰ 3-Amino-6-diethylamino-9-phenylphenazinium chloride (Heliotrope BS) (18.9g) was dissolved in 350ml of hot water at 80°C. To the solution cooled to 70°C was added 350 ml of toluene, followed by 43.5 g of sodium dithionite and 20g of a 20% aqueous NaOH solution. The mixture was stirred vigorously and purged with a stream of nitrogen. After the color of the solution had completely discharged, 13 ml of glacial acetic acid was added to give a pH of 4 and 15.3 g of salicylaldehyde was added over 30 min at 60°C. The mixture was stirred at that temperature for 3 h and cooled down, then 9 g of NaOH was added, followed by 26.1 g of 2-trifluoromethyl-benzoylchloride over 1 h at 20–30°C. The mixture was stirred for 3 h and filtered. The filtrate was separated and the toluene layer was stirred with 250ml of 1 N hydrochloric acid for 30 min at 30–35°C to hydrolyze the imine. The aqueous layer was also stirred with 1 N HCl. The combined aqueous layers were washed with chloroform and neutralized with NaOH. The precipitate was extracted with 150ml of toluene and the organic layer was washed with water, dried, treated with activated charcoal, and concentrated to dryness. The residue was recrystallized to yield 14.9 g of 3-amino-6-diethylamino-9-phenyl-10-(2-trifluoromethylbenzoyl)-9,10-dihydrophenazine having a melting point of 139.5–143°C.

Synthetic method 11: 3-(N-benzyl-N-methyl)amino-9-ethyl-10-benzoyl-9,10-dihydrophenazine (62) (procedure from EP Patent Application 671,393).²¹ 9-Ethylphenazinium ethosulfate (58) (obtained from phena-



zine and diethylsulfate) (62 g) was dissolved in 2.5 liters of water and 125 g of potassium ferricyanide was added, then 327 ml of a 10% aqueous NaOH was added slowly. The solution turned dark red. After standing overnight, 300ml of a 40% aqueous NaOH was added. The resulting precipitate was

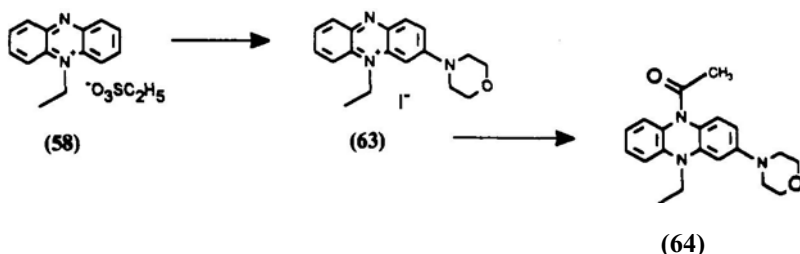
collected by filtration, washed with water, and dried to give 36.42g (88%) of 9-ethyl-3-phenazinone (**59**).

Seventeen grams of phenazinone **59** was dissolved in 80ml of phosphoryl chloride. Phosphorous pentachloride (15.6 g) was added and the mixture stirred for 2 h. The product (chloride salt) was collected by filtration, washed with ether, and dried. This solid was dissolved in 500ml of water, filtered to remove some insoluble tar, and 17.9g of potassium iodide was added to precipitate the iodide. The product was collected by filtration, washed with water, and dried *in vacuo* to yield 19.9g (71%) of 3-chloro-9-ethylphenazinium iodide (**60**).

The chlorophenazinium salt **60** (15.5 g) was dissolved in 2.5 liters of acetonitrile, filtered, and 12.6 g of benzylmethylamine was added. The mixture was stirred for 20h and solvent was removed by rotary evaporation. The resulting solid was dissolved in 600ml of ethanol and reprecipitated by pouring into 3 liters of ether to yield 11.1 g (58%) of the magenta dye 3-(*N*-benzyl-*N*-methyl)amino-9-ethylphenazinium iodide (**61**).

Twelve grams of the magenta dye **61** was dissolved in 250ml of methylene chloride and stirred gently with a solution of 12.2g of sodium dithionite in 250 ml of water. A solution of 5 g of benzoyl chloride in 10 ml of dichloromethane was added slowly to the lower organic layer. The pH of the upper aqueous layer was maintained at 5 to 6. The organic layer was separated, washed with dilute aqueous NaOH and brine. The solution was absorbed onto silica gel and rotary evaporated to dryness. The product was washed from the silica with ether. The ether solution was evaporated to yield 8.2 g of the leuco dye 3-(*N*-benzyl-*N*-methyl)amino-9-ethyl-10-benzoyl-9,10-dihydrophenazine (**62**).

Synthetic Method 12: 3-morpholino-9-ethyl-10-acetyl-9,10-dihydrophenazine (65) (procedure from EP Patent Application 671,393).²¹ 9-Ethylphenazinium ethosulfate (**58**) (7.69 g, 23 mmol) was weighed into a 1-liter three-necked round-bottom flask and dissolved completely in 400 ml of ethanol. Air, dried by passage through concentrated sulfuric acid, was bubbled through the solution. Morpholine (2.0 g, 23 mmol) was then run into the stirred solution. A magenta dye began to form immediately. After 2 h of air bubbling through the solution, solvent evaporation gave a tar which crystallized on standing. The ethosulfate salt was dissolved in 750 ml of water and the stirred solution treated with 250g of sodium iodide. Stirring was continued for 30 min. The precipitate was collected by filtration, washed with a little cold water, and then with a minimum volume of acetone, and dried *in vacuo* at 70°C to afford 6.51g (67%) of the dye 3-morpholino-9-ethylphenazinium iodide (**63**): $\lambda_{\max}(\text{EtOH})$ 526 nm (ϵ 1.62×10^4).

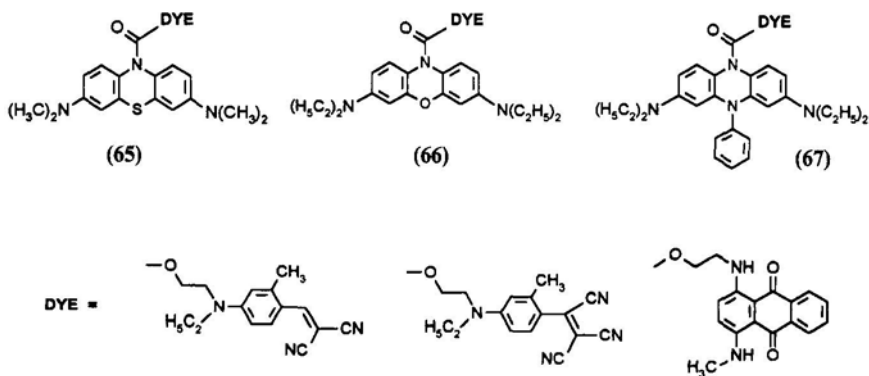


The above dye **(63)** (0.1264g, 3 mmol) and 0.261 g (4 mmol) of zinc powder was weighed into a 100ml round-bottom flask, which was sealed with a rubber septum and purged with a stream of nitrogen. Anhydrous tetrahydrofuran (20 ml) was introduced and the suspension was degassed for a further 30 min. Glacial acetic acid (0.223 g, 4 mmol) was introduced by syringe. On stirring vigorously, the color of the solution faded to a yellow solution. After 30 min, 0.44 g (4.3 mmol) of triethylamine was added, followed by 0.77 g (10 mmol) of acetyl chloride. The solution was left to stir overnight at room temperature under nitrogen. After 19 h, 1 g (10 mmol) of triethylamine was added by syringe. Water (10 ml) was then added slowly, followed by 20 ml of chloroform. The mixture was exposed to air only, once this point had been reached. The aqueous phase was separated, filtered, and washed once with 20 ml of chloroform. The combined organic extracts were washed with water (3×25 ml) until no trace of dye remained, then dried over magnesium sulfate. Solvent evaporation gave an oil (1.117 g) which crystallized on standing. Recrystallization from ethylacetate–ether afforded 0.5 g (56%) of the leuco dye 3-morpholino-9-ethyl-10-acetyl-9,10-dihydro-phenazine **(64)** as faintly colored platelets (mp 161–162°C).

3.5. DYE RELEASE DEVELOPERS

3.5.1. Introduction

The leuco dyes of this new class are peculiar in that they are capped at their 10-position by another dye moiety. They are in fact colored leuco dyes which on oxidation are split into two different dye fragments: one of the dyes is destined for the receptor sheet while the oxidized leuco hopefully remains on the donor sheet. The capping dye is selected among sublimable dyes whereas the azine dyes being cationic in nature would be less mobile. They have been developed to address some problems encountered in thermographic and photothermographic systems.²⁴ Representative examples of this class of leuco dye developers are compounds **65**, **66**, and **67**.

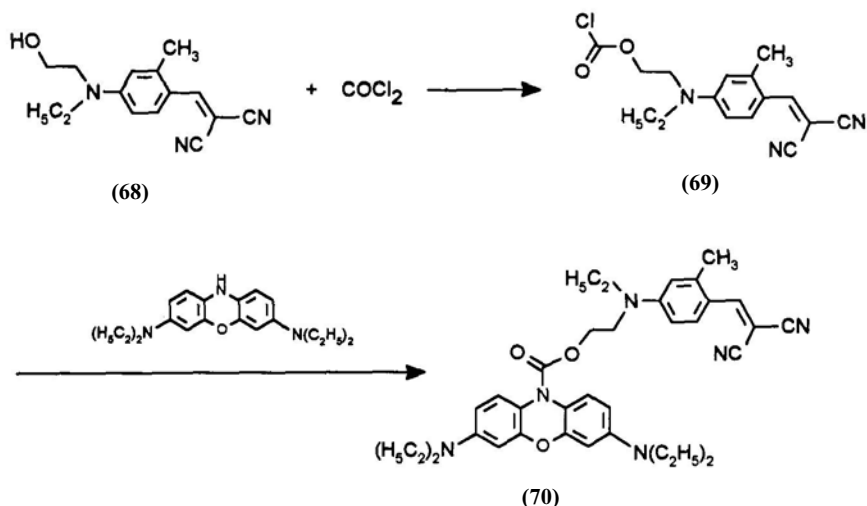


The thiazine, oxazine, and phenazine leuco dyes that generate yellow, magenta, and cyan dyes are used in conjunction with an oxidant such as metal nitrate or silver halide in a multilayer construction to form the basis of a very simple multicolor imaging system. Two main drawbacks are the different reactivities of the various leuco dyes and the presence of unreacted leucos in the final image which lead to high image background caused by air oxidation. There has been a great interest in transferring the dye image to a receptor to achieve a clean and stable color image leaving behind unwanted by-products. Numerous dye developers, not necessarily related to leuco dyes, have been described whereby the three primary dyes (Y, M, C) are linked to a common type of developer to ensure that the three colors are generated at the same rate.²⁴ The developer is immobilized with hydrophobic long ballasting groups and the transferable dyes are usually small and highly mobile.

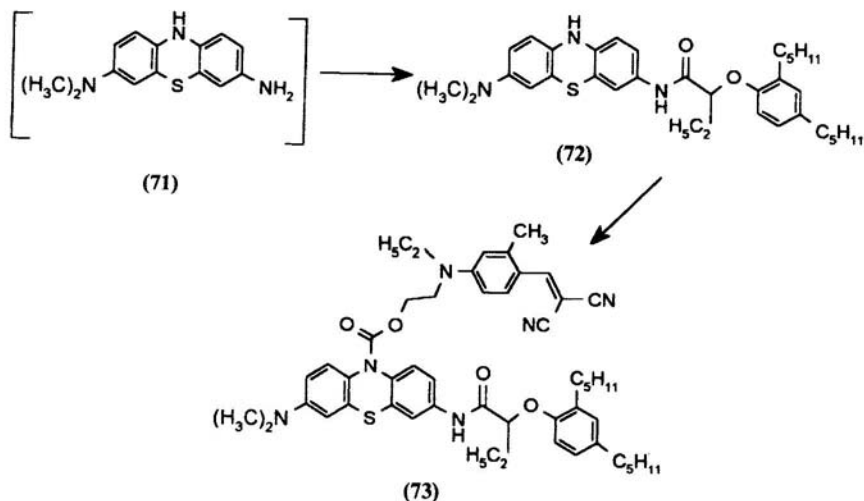
The characteristics of the azine leuco dyes have been adapted to the development of this new class of leuco dye developers. Sublimable or diffusible dyes are used to cap the 10-position of the leuco thiazine, oxazine, or phenazine dye where the splitting takes place as a result of imaging. The leuco dye moieties are rendered less mobile with long aliphatic chains.

3.5.2. Synthetic Methods

Leuco Methylene Blue, Basic Blue 3, or phenazine dyes are capped with a dye bearing acid chloride or chlorocarbonyl functionality. Normal procedures employed for the synthesis of benzoyl leuco Methylene Blue can be utilized except that a dye chloroformate (69) replaces the benzoyl chloride.

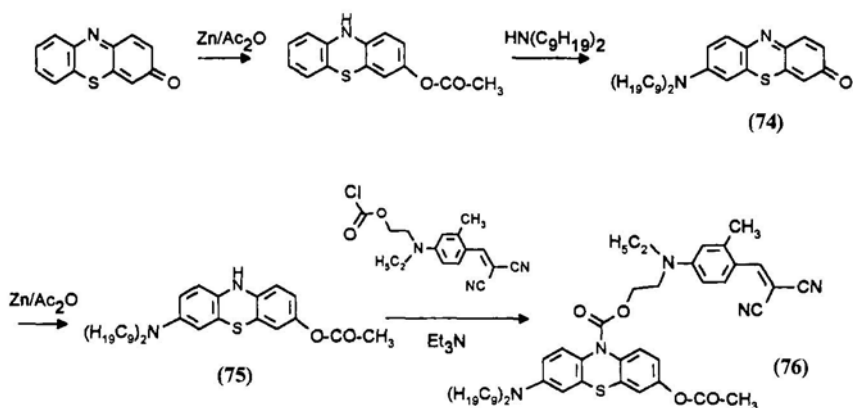


The exocyclic amino group of Azures **A** or **B** can be used to attach a long aliphatic ballasting group. Under mild reaction conditions, the ring amino group at the 10-position being much less reactive remains unsubstituted. The dye capping is effected at reflux temperatures in an organic solvent.



Azure A can be reduced to an air sensitive intermediate **71** and acylated in one step to produce the ballasted leuco **72** which can be isolated and capped with the dye chloroformate **69** to give the ballasted yellow dye release developer **73**.

Derivatives of Methylene Violet **6** possessing long aliphatic chains are obtained by oxidative coupling of 3-acetoxyphenothiazine with a secondary amine in the presence of an oxidant such as iodine. The oxidative coupling of phenothiazine with amine is well known but in this case the reaction does not stop there but proceeds further at reflux temperatures to the phenothiazinone **74**.⁹ Reduction of the latter dye and treatment with acetic anhydride yields the ballasted phenothiazine **6**. Reaction of **75** with the dye chloroformate **70** yields the ballasted leuco dye developer **76**.



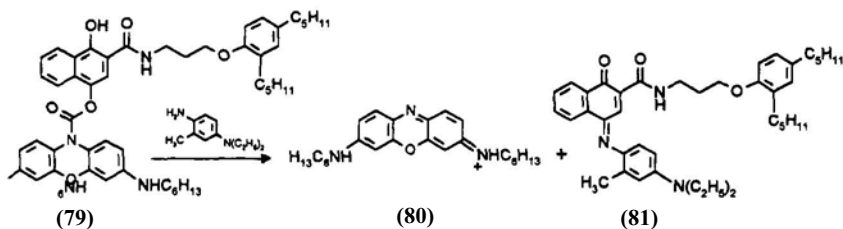
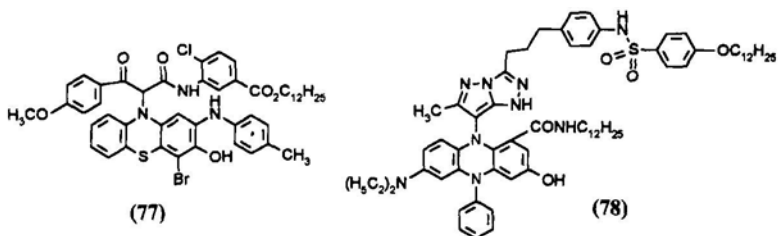
Synthetic Method 13: 4-{ethyl-[2-(3,7-bisdiethylaminophenoxazinyl)-carbonyloxyethyl]amino}-2-methylphenylmethylenepropanedinitrile(**70**) (procedure from US. Patent 4,981,775).²² The yellow dye {[4-ethyl-(2-hydroxyethylamino)]-2-methylphenyl}methylenepropanedinitrile (**68**) (2.55 g, 0.01 mol) was dissolved in 70ml of dichloromethane and phosgene 12.5% w/w solution in toluene (16 g, 0.02 mol) was added. After stirring for 2 h at room temperature, the solvent was evaporated and the residue recrystallized from a mixture of dichloromethane-ether to give 3 g of the dye chloroformate **69** as yellow leaflets.

Basic Blue 3 (Aldrich Chemical Co., 85% pure: 12.7 g, 0.03 mol) was dissolved in 200ml of water and 200ml of dichloromethane was added to

form a two-phase mixture. The mixture was stirred gently under nitrogen gas and the pH was adjusted to 10 with a 40% aqueous NaOH solution. Sodium dithionite (6.75 g, 0.033 mol) in 100ml of water was added and the mixture stirred for 10 min as decoloration took place. The pH was readjusted to 6 and a solution 7.7 g (0.03 mol) of the dye chloroformate **69** in 100ml of dichloromethane was then added in one portion. The mixture was stirred for $2\frac{1}{2}$ h, the pH being continuously adjusted to 6 with 40% aqueous NaOH solution. The pH was raised to 10 and the mixture was filtered through a shallow plug of Hyflo Supercel filter aid. The organic layer was separated, washed with brine, and dried over magnesium sulfate. Silica gel 60 (10g) was added to the dried solution and the filtered solution was then concentrated to dryness to yield a yellow-brown foamy solid (15.9 g). The solid was triturated with 250ml of boiling isopropanol and dried to yield 14.24 g of the dye-capped leuco **70**.

3.6. LEUCO DYE DEVELOPERS

Dye release developers are themselves colored molecules, the presence of which in silver halide photographic materials could interfere with light capture by the light-sensitive silver halide. Less light would be available to the sensitizing dyes. Another approach has been reported in which the leuco dye is linked to the coupling-off position of conventional photographic color



developers.²⁵ The leuco dye developers obtained, illustrated by compounds **77**, **78**, and **79**, would in theory be colorless. After light exposure and development with a *p*-amino-phenylenediamine-type color developer, two dyes would be generated. The yellow leuco dye developer **77** would give rise to two yellow dyes whereas the magenta leuco developer **78** would generate two magenta dyes. The cyan leuco dye developer **79** would give rise to two cyan dyes **80** and **81**, for example. Since two dyes are generated for every photon absorbed, this could form the basis for a method of image amplification. In practice, leuco dyes are not always colorless. Some leuco dyes retain a residual visible color, either yellowish or pinkish, which will add to the background. Image print-out due to premature air oxidation needs to be considered.

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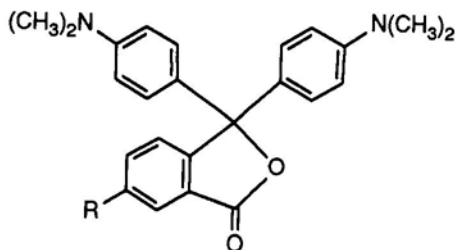
4

Synthesis and Properties of Phthalide-Type Color Formers

IAN J. FLETCHER and RUDOLF ZINK

4.1. INTRODUCTION

Considering the fact that 3,3-bis(4-dimethylaminophenyl)phthalide (1), commonly known as Malachite Green lactone, was reported¹ well over 100 years ago, it is somewhat surprising to realize that the analogous 6-dimethylaminophthalide [Crystal Violet lactone (CVL)] (2) was not described until 1945,² and that the vast majority of references cited herein are considerably more recent.

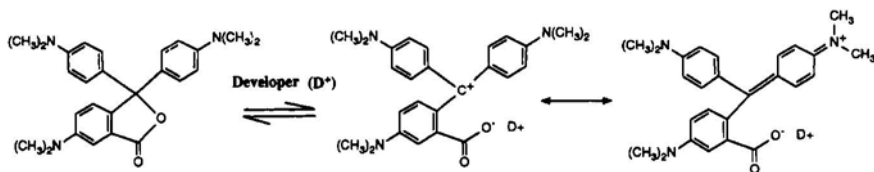


(1) R = H

(2) R = N(CH₃)₂

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Chemistry and Applications of Leuco Dyes, edited by Muthyala. Plenum Press, New York, 1997.



Scheme 1

The driving force for this development followed the introduction of carbonless copying paper into the marketplace by the National Cash Register Company (NCR) in 1954. The principles of this system have long been described,^{3,4} and it suffices to demonstrate the color-forming reaction of CVL in Scheme 1.

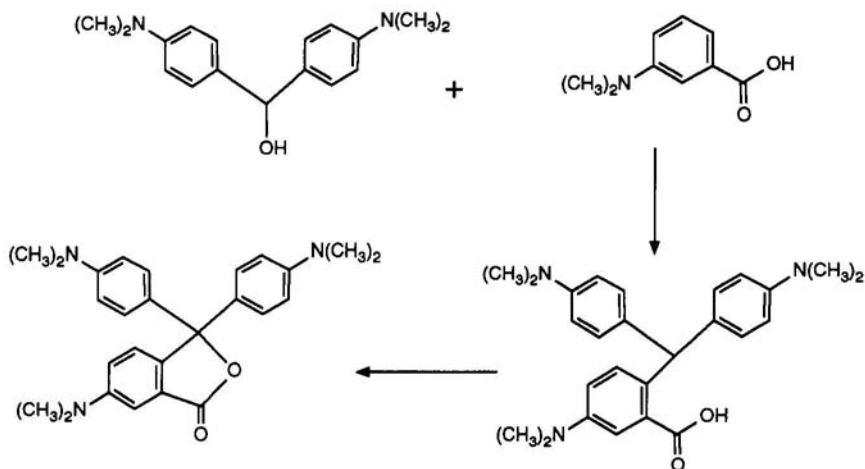
On reaction of the electron-donating colorless phthalide (color former or dye precursor) with an electron-accepting color developer, reversible opening of the lactone ring occurs, yielding the resonance-stabilized cationic dye. Hence, it is obvious that the properties of the color former also are dependent on those of the developer, but this is a complex problem and hardly the subject of this article. However, where important differences arise these will be referred to, and thus, it is necessary to briefly mention the various types of developers utilized in present-day carbonless copying papers. Originally NCR employed Attapulugus clay as developer but this has been superseded by phenol-formaldehyde resins in the United States. In Europe, however, inorganic developers, particularly bentonite, are of prime importance, whereas in Japan, substituted zinc salicylates prevail.

In the years following the introduction of carbonless papers there has been a requirement for shades differing from the original royal blue, in particular a black script. This has resulted in the development of color formers possessing shades covering the entire visible spectral range. Phthalides are particularly versatile in this respect and in the following we shall attempt to describe their varying syntheses and the effects of substitution on their properties.

4.2. ARYLMETHANE PHTHALIDES

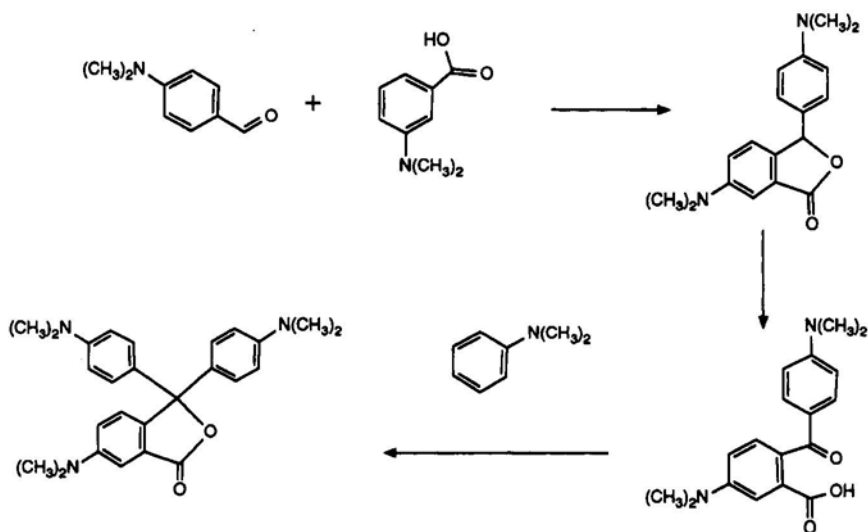
4.2.1. Triarylmethane Phthalides

Since the introduction of carbonless copying papers, CVL has undoubtedly found the most widespread use as a phthalide color former. Hence, it is appropriate to describe in detail the various approaches to its synthesis, particularly as they are representative of the preparations of various other phthalides described herein.



Scheme 2

The first synthesis of CVL, as described by NCR,² is shown in Scheme 2. The condensation of 4,4-bisdimethylaminobenzhydrol with 3-dimethylaminobenzoic acid was accomplished in 90% sulfuric acid to yield 2-(4,4-bisdimethylaminobenzhydryl)-5-dimethylaminobenzoic acid (leuco CVL), which was subsequently oxidized to CVL using lead dioxide in dilute mineral acid. Since this time, numerous variations on both reaction conditions and also reagents employed for this synthesis have been described. For example, it has been shown⁵ that both yield and quality of the intermediate leuco CVL may be improved by carrying out the initial condensation in dilute mineral acid, whereby the particle size of the benzhydrol has also been claimed⁶ to be of importance. The oxidation step has been carried out using potassium permanganate,⁷ potassium persulfate,⁸ potassium ferricyanide,⁹ or chloranil in the presence of a metal complex catalyst.¹⁰ However, the method of choice would appear to be the use of hydrogen peroxide in basic solution,¹¹⁻¹⁴ catalyzed by copper or cobalt complexes,¹⁵ chromium, iron, manganese, or vanadium salts¹⁶ and iron or manganese chelates¹⁷ having been claimed to be advantageous. Furthermore, the oxidation has been effected using air or oxygen in the presence of cobalt or manganese complexes,¹⁸ acetic acid,¹⁹ or iron, copper, or cobalt salts in acidic media.²⁰ One further variation on the above synthesis has been the replacement of 4,4'-dimethylaminobenzhydrol by other substrates. The corresponding amino derivative, leucauramine, has also been found²¹ to react analogously, while the direct formation of leuco CVL by condensation of *N,N*-dimethylaniline, 4-dimethylaminobenzaldehyde, 3-dimethylaminobenzoic acid, and urea in strong acid has been reported.²² Finally, urea has been reacted



Scheme 3

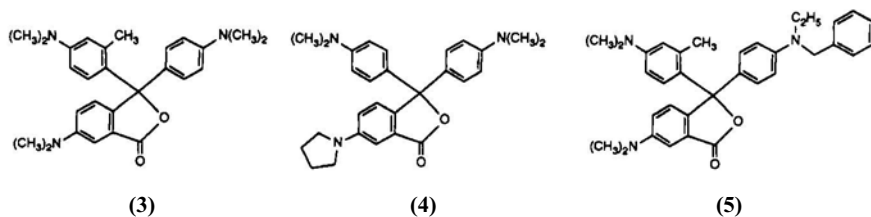
with 4-dimethylaminobenzaldehyde and *N,N*-dimethylaniline to yield a mixture of mono- and bis(4,4'-dimethylaminodiphenylmethyl) ureas which also yield leuco CVL on reaction with 3-dimethylaminobenzoic acid.²³

The most versatile route to lactone color formers is based on the elegant synthesis of Malachite Green lactone described by Haller and Guyot in 1899.²⁴ Scheme 3 illustrates the application of this route for the preparation of CVL.

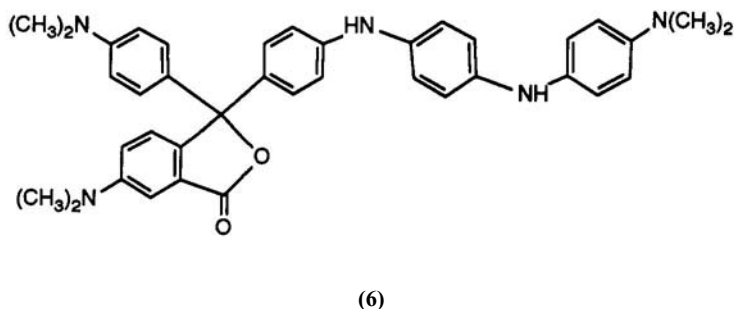
4-Dimethylaminobenzaldehyde condenses with 3-dimethylaminobenzoic acid in the presence of acetic anhydride to yield 3-(4-dimethylaminophenyl)-6-dimethylaminophthalide.²⁵ Subsequent oxidation, preferably with 3-nitrobenzenesulfonic acid,²⁶ yields the bisdimethylaminobenzophenone-carboxylic acid, which then is treated with dimethylaniline in acetic anhydride to form CVL.^{26,27} A variation for the preparation of the intermediate phthalide by treatment of 2-formyl-5-dimethylaminobenzoic acid with dimethylaniline has also been described.²⁸ However, the difficulty in preparing this former starting material renders this route less attractive. It has also been shown²⁹ that treatment of the phthalide intermediate with dimethylaniline in the presence of a Friedel-Crafts catalyst yields leuco CVL, which may then be oxidized as described for Scheme 2. The development of CVL as a color former for carbonless copying papers was a result of the deficiencies of the readily available Malachite Green lactone, orig-

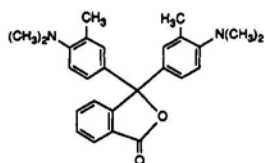
inally prepared¹ by condensation of phthalic anhydride with dimethylaniline in the presence of zinc chloride, as a color former. The green color was unsuitable³⁰ and the intensity of the image insufficient with certain developers. The introduction of the dimethylamino group into the 6-position results in a blue image with increased intensity.

However, despite the commercial importance of CVL as a color former, the product possesses a number of disadvantages, notably poor lightfastness especially in combination with clay developers, and low solubility in organic solvents. Hence, it is not surprising that a vast number of variations on the basic structure have been described in the patent literature, typical examples of which are structures 3–5 (see also for example Ref. 26).

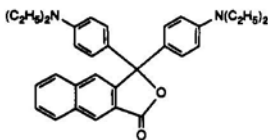


Compounds 3 and 4 are claimed^{31,32} to exhibit good solubility, while 5 is stated³³ to possess excellent light-resistance. However, to date, no similar product has been able to replace CVL in the marketplace. One further example of the flexibility of the synthetic route in Scheme 3 is the preparation of compound 6,³⁴ which is reported to show light absorption in the near infrared region and is thus suitable for recordings readable by lasers.

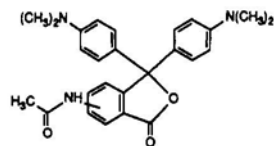




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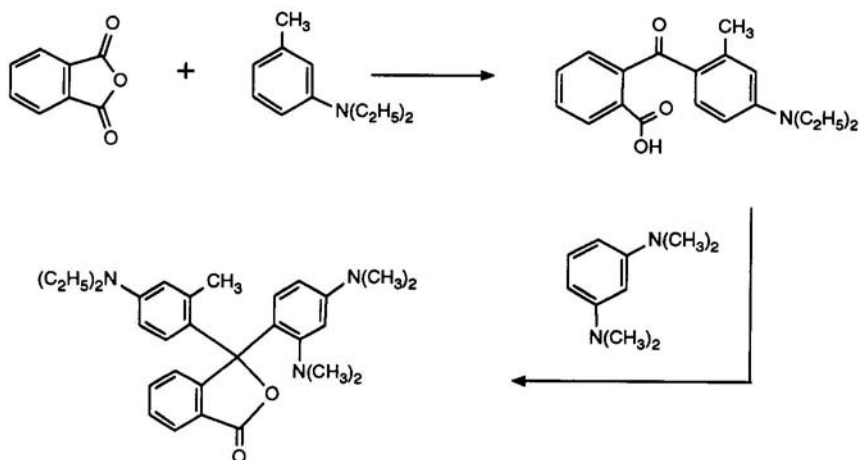


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The introduction of the dimethylamino group into the phthalide ring has, however, not been the sole attempt to modify the properties of Malachite Green lactone. Early attempts resulted in the preparation of compounds such as **7–9**. Compounds **7** and **8** were prepared by condensation of the appropriate amine with phthalic anhydride³⁵ and 2,3-naphthoic anhydride,³⁶ respectively, with the appropriate aniline in the presence of zinc chloride. Compound **9** was prepared by nitration of Malachite Green lactone, yielding a mixture of isomers which were subsequently reduced and acetylated.³⁷ None of these modifications, however, gave rise to the required blueshift. It is perhaps noteworthy that reductive alkylation of a mixture of nitromalachite green lactones with palladium on charcoal and formaldehyde has been proposed³⁸ as a synthetic route to CVL. This process, however, is clearly of little synthetic value since it not only yields mixtures, but also reduces the lactones to the leuco compounds which subsequently must be reoxidized.

It thus became clear that the improvement in properties of CVL as opposed to Malachite Green lactone was due to the electron-donating effect of the dimethylamino group in the 6-position of the phthalide ring. On this basis a far superior approach to that above was the incorporation of additional electron donors into the dialkylaminophenyl groups.³⁹ Scheme 4 demonstrates the synthetic route to such compounds.

Phthalic anhydride condenses with the aniline derivative in the presence of zinc or aluminum chlorides to yield the intermediate benzoyl-benzoic acid, which subsequently reacts with 1,3-bis-*N,N*-dimethylaniline in acetic anhydride to yield the phthalide. The above compound gives a violet-gray image when applied to a clay developer. Clearly this synthesis is also very flexible and variations in shades of color formers have been obtained by varying the aniline components and also by using phthalic anhydrides substituted, for example, by nitro groups or chlorine atoms. Such products have excellent properties as color formers and have been used commercially. Furthermore, this synthetic route is of great importance for the preparation of heterocyclic substituted phthalides, as will be seen later.

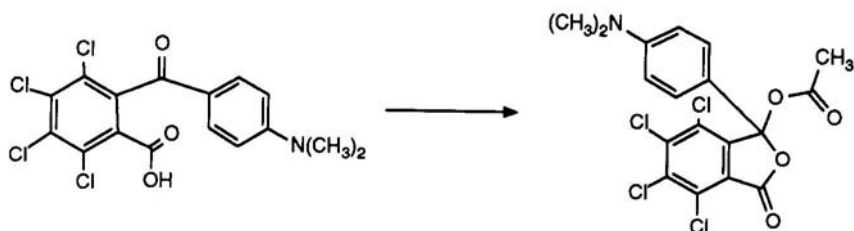


Scheme 4

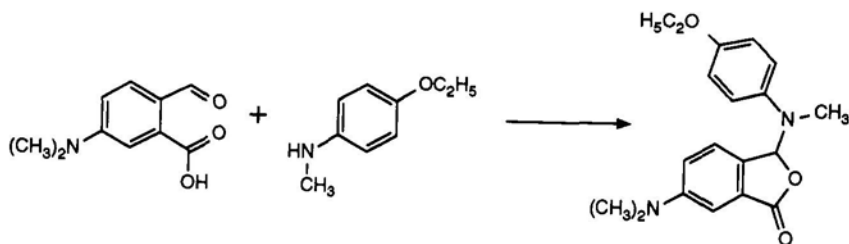
4.2.2. Diarylmethane Phthalides

In order that diarylmethane phthalides function as color formers, it is necessary to replace the hydrogen atom in the 3-position of the phthalide ring by an electronegative group. Scheme 5 typifies the synthetic route to such phthalides. Once again the key intermediate is the carboxybenzophenone which, on treatment with acetic anhydride, yields the 3-acetoxypthalide.⁴⁰ Treatment with alkylamines,⁴¹ anilines,⁴² or diphenylamines⁴³ leads to the formation of the corresponding 3-amino-substituted phthalides. Finally, ethers and thioethers have also been reported,⁴⁴ being obtained by reaction of the benzophenone first with thionyl chloride followed by an alcohol, phenol, or thiophenol.

All of these phthalides in which the phthalide ring is not substituted by electron-donating groups are yellow to orange color formers, and useful as



Scheme 5



Scheme 6

shading components for the production of black images. However, introduction of a dialkylamino group into the 6-position of the phthalide ring results in bluish-green shades.

4.2.3. Monoarylmethane Phthalides

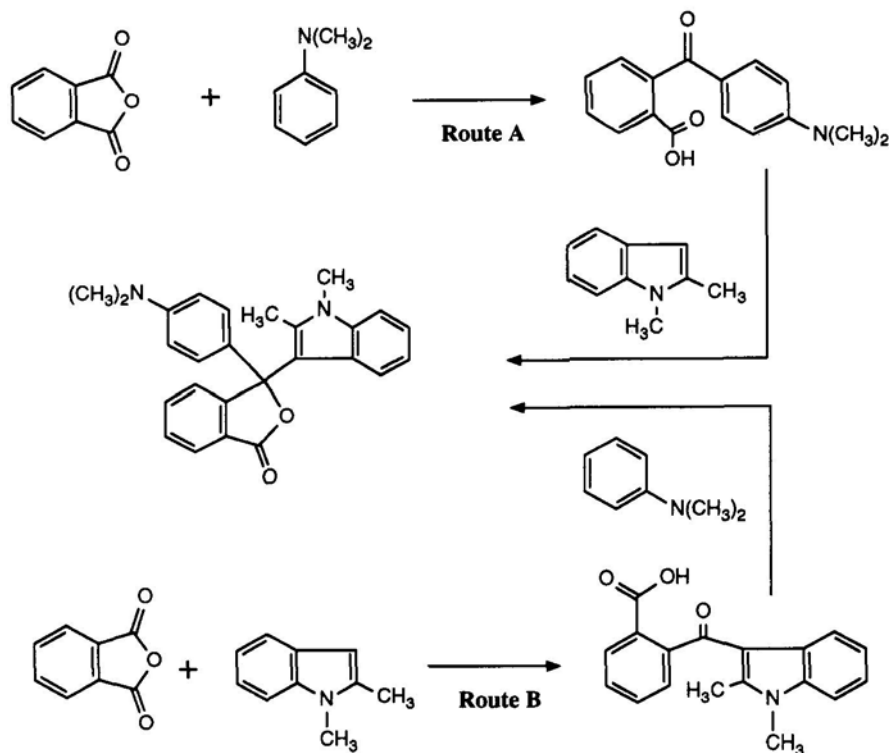
Only one report⁴⁵ of monoarylmethane color formers has appeared to date, the synthetic route being shown in Scheme 6. These compounds in combination with clay developers give yellow images with good light stability.

4.3. MONOHETEROCYCLIC SUBSTITUTED PHTHALIDES

4.3.1. 3-Heterocyclic Substituted Phthalides

A different approach for the modification of the basic Malachite Green lactone structure has been the replacement of one 4-dimethylaminophenyl group by electron-rich heterocycles. The most thoroughly investigated heterocycle has been the 3-indolyl residue, which may be introduced by two different routes as shown in Scheme 7.

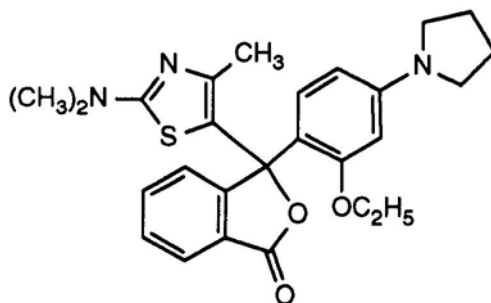
The first compounds of this class⁴⁶ have been obtained via Route A. The initial condensation of phthalic anhydride with dimethylaniline requires a Friedel–Crafts catalyst, while condensation of the resulting benzophenone with the indole requires acetic anhydride. For Route B preparation of the intermediate 1,2-dimethyl-3-(2-carboxybenzoyl)indole has also been described⁴⁷ by condensation of the two components in the presence of aluminum chloride. However, in our experience, aluminum chloride is, in this case, unnecessary, thus rendering this route the method of choice.



Scheme 7

These indolylphenylaminophthalides are blue color formers with generally good light stability. Due to their ease of synthesis, it is not surprising that a large number of variations have been reported. For example, the phthalide ring has been substituted by dimethylamino groups,⁴⁸ nitro-groups,⁴⁹ or chlorine atoms⁵⁰ to produce slightly varying shades, while long-chain alkyl groups have been attached to the indole nitrogen atom to improve solubility.⁵¹

In addition to indolylphthalides, other heterocyclic phthalides such as pyrrol-2-yl- and carbazol-3-yl-dialkylaminophenyl phthalides have also been prepared by analogous synthetic procedures.^{48,52} Depending on the other substituents in the molecule and the developer used, the pyrrolyl color formers exhibit red to blue shades, while the carbazolyl compounds can vary from violet to green. Replacing the indole by 2-dimethylamino-4-methylthiazole in Route A leads to color formers such as **10**.⁵³ Compound **10** forms a green image in combination with a clay developer.

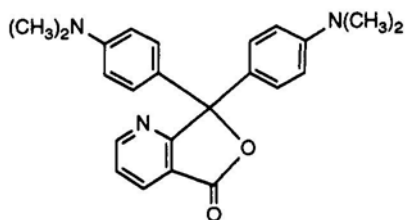


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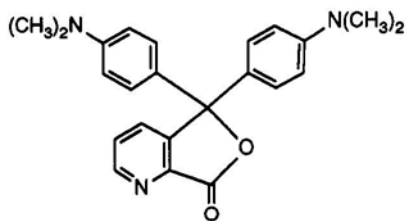
4.3.2. Diarylmethylazaphthalides

Another approach to improve the color formation properties of Malachite Green lactone has been the introduction of nitrogen atoms into the phthalide ring. Thus, condensation of pyridine-2,3-dicarboxylic acid anhydride with dimethylaniline in the presence of zinc chloride has been shown⁵⁴ to yield a mixture of the 4- and 7-azaphthalides **11** and **12**.

Stepwise addition of the aniline moieties in analogy to Scheme 7 (Route A) allows the preparation of asymmetrically substituted derivatives.^{55,56} The use of pyridine-3,4-dicarboxylic acid anhydride similarly results in the formation of mixtures of 5- and 6-azaphthalides.⁵⁷ Quinoline-2,3-dicarboxylic anhydride has also been converted into the corresponding azaphthalides in a similar manner.⁵⁸ Pyrazine-2,3-dicarboxylic acid anhydride yields



(11)



(12)

4,7-diazaphthalides,⁵⁹ and quinoxaline-2,3-dicarboxylic acid anhydride has also been shown⁶⁰ to react analogously.

These azaphthalides have been reported to give blue or greenish-blue images, together with clay developers, and to have good color forming ability and resistance toward light and moisture.

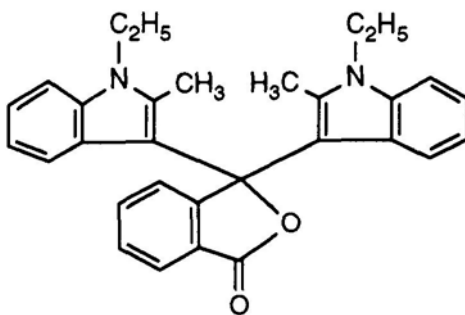
4.4. BISHETEROCYCLIC SUBSTITUTED PHTHALIDES

4.4.1. 3,3-Bisheterocyclic Substituted Phthalides

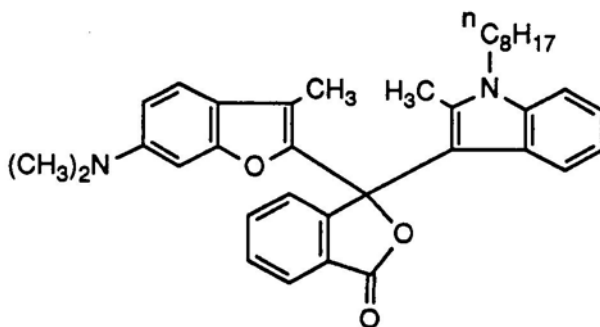
From a commercial viewpoint the most important compounds of this class are the 3,3-(bisindol-3-yl)phthalides. The first synthesis⁴⁷ involved Route B as described in Scheme 7, in which a second indole derivative condenses with the indolylbenzoylbenzoic acid in acetic anhydride. However, for the preparation of symmetrical derivatives it has been shown⁶¹ that a one-pot process, avoiding isolation of the intermediate and use of aluminum chloride, is more convenient.

Bisindolylphthalides such as **13** are red color formers with excellent fastness properties and are used commercially as shading components for the production of black images. Variations on this structure are possible. For example, the introduction of long-chain alkyl groups at the indole nitrogen atoms improves solubility,⁶² and substitution of the phthalide ring by 5- or 6-dimethylamino groups⁶³ or by four chloride atoms⁶⁴ results in purple color formers.

Reaction of the indolylbenzoylbenzoic acid with electron-rich heterocycles other than indoles has also produced a number of novel color



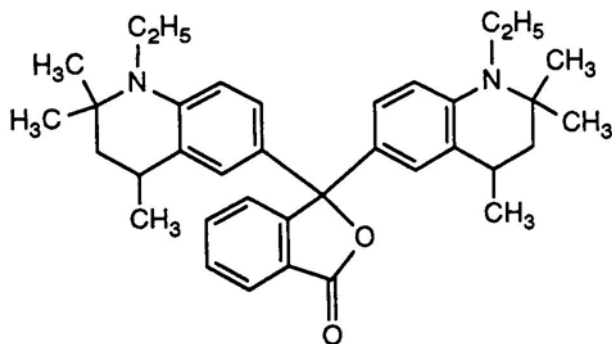
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(14)

formers. Thus, carbazoles^{63,64} have been condensed to yield purple color formers, while indolizines⁶⁵ result in purple to blue images. A vast number of other bridgehead nitrogen-containing heterocycles such as imidazo-[2,1-*b*]thiazoles have also been condensed⁶⁶ leading to color formers producing red to blue images, while 6-dimethylamino-2-methylbenzofuran results in **14**, a green color former.⁶⁷

Finally, a number of heterocycles such as quinolines, indoles, and diazines in which the heterocyclic ring is hydrogenated have been reacted as shown in Scheme 7 to produce a number of green color formers such as **15**.⁶⁸



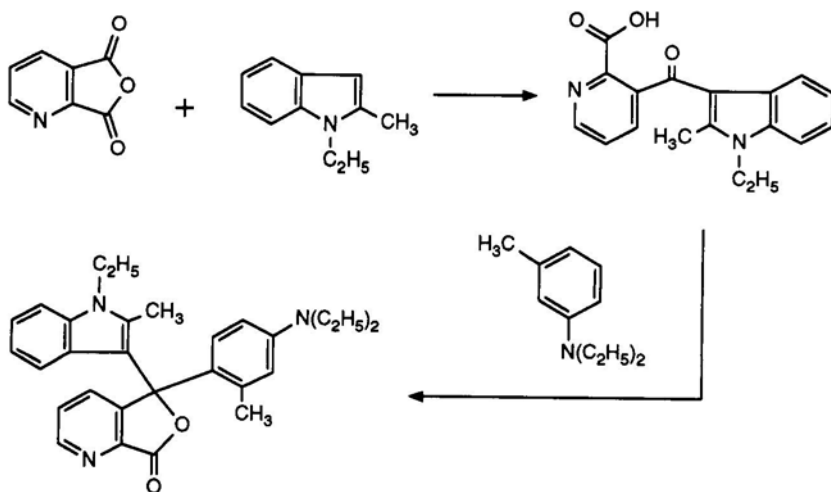
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4.4.2. 3-Heterocyclic Substituted Azaphthalides

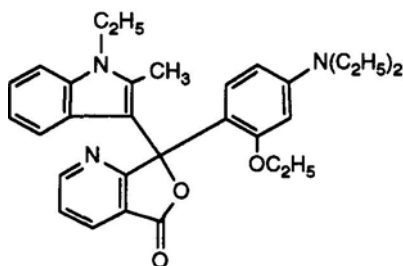
As in the previous section, one class of compounds, namely, the 3-dialkylaminophenyl-3-indolyl-4-azaphthalides, is of primary importance from a commercial viewpoint. The 7-azaisomer, the first dialkylaminophenylindolylazaphthalide, has been prepared⁶⁹ as shown in Scheme 8 (cf. Scheme 7).

Heating pyridine-2,3-dicarboxylic acid anhydride with 1-ethyl-2-methylindole has been claimed to yield solely the pyridine-2-carboxylic acid, albeit in low yield. This then clearly reacts with *N,N*-diethyl-3-toluidine in acetic anhydride to give the 7-azaphthalide. This is surprising in view of a later report⁷⁰ in which a one-pot process has been described. Heating pyridine-2,3-dicarboxylic anhydride, prepared *in situ*, with the indole and subsequent reaction with 3-*N,N*-diethylamino-phenetol under identical conditions to those used in Scheme 8 (but without intermediate isolations) produced a 20:1 mixture of the 4- and 7-azaisomers **16** and **17**. It appears that in the previous report the major intermediate isomer, the pyridine-3-carboxylic acid, has not been isolated.

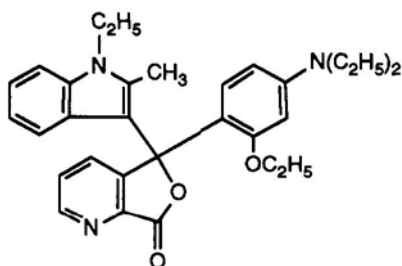
Color formers such as **16** and **17** and their mixtures are commonly known as "Pyridyl Blues" and are excellent products in combination with organic developers, yielding intense blue images with very high fastness properties. However, it has been observed⁷¹ that, for some applications, the 7-azaisomer is too reactive and hence it was desirable to modify the



Scheme 8



(16)



(17)

synthesis to produce solely the 4-azacomound **16**. It was later discovered⁷² that the addition of catalytic quantities of metal salts such as zinc or aluminum chlorides during condensation of pyridine-2,3-dicarboxylic acid anhydride with indole leads solely to formation of the pyridine-3-carboxylic acid, consequently achieving the desired result of eliminating formation of the 7-azaisomer. It is interesting to note that, when the 2-position of the indole ring is unsubstituted, the use of a large excess of aluminum chloride in the initial condensation is reported⁷³ to lead to exclusive formation of the 7-azaisomer.

Due to the commercial importance of the Pyridyl Blues, it is not surprising that a considerable number of structural variants have been patented. Variations in the aniline part of the molecule have included diarylaniline,⁷⁴ long-chain alkoxy-substituted anilines,⁷⁵ cyclohexylanilines,⁷⁶ and amino-substituted anilines,⁷⁷ while long-chain alkyl groups have also been attached to the indole nitrogen atom.⁷⁸ Compounds carrying substituents in the pyridine ring have also been reported.⁷⁹

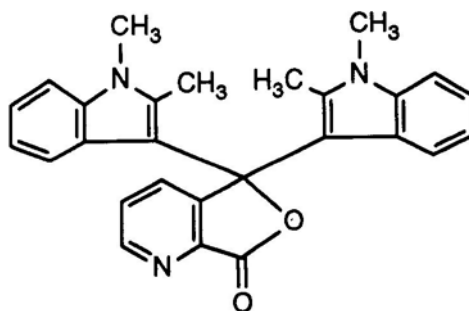
Replacement of the pyridine-2,3-dicarboxylic acid anhydride by the corresponding 3,4-dicarboxylic acid anhydride leads to formation of approximately 1 : 1 mixtures of the 5- and 6-azaisomers.⁸⁰ These blue color formers are suitable for use with all types of developers. A number of heterocycles other than indoles have also been used to provide novel color formers. Thus, carbazoles, acridines, and tetrahydroquinolines have all been shown⁸¹ to yield the corresponding 4- and 7-azaphthalides as color formers. Indolizines give rise to green color formers,⁶⁵ while bridgehead nitrogen heterocycles such as imidazo[1,2-*a*]pyridines produce 4-azaphthalides⁶⁶ forming blue images.

Pyrazine-2,3-dicarboxylic acid anhydride has also been shown⁶⁹ to react according to Scheme 8, yielding 4,7-diazaphthalides very similar in

their properties to the Pyridyl Blues, as is the case with quinoxaline-2,3-dicarboxylic acid anhydride,⁸² which also has been reacted⁶⁶ with imidazo-[1,2-*a*]pyridines to produce green color formers.

4.5. 3,3-BISHETEROCYCLIC SUBSTITUTED PHTHALIDES

The possibility of replacing all three phenyl rings in the triarylmethane lactone structure by heterocycles has also been exploited. The first compound to be described⁸³ was the 3,3-bisindolyl-7-azaphthalide (**18**). This

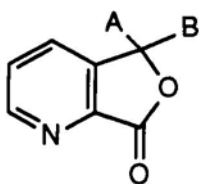


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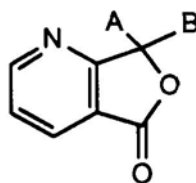
compound was obtained directly by reaction of 2 mol of 1,2-dimethylindole with pyridine-2,3-dicarboxylic acid anhydride in acetic anhydride. However, the unambiguity of this 7-azaisomer would seem somewhat doubtful since a later report⁸⁴ describes the preparation of 4- and 7-azaisomeric mixtures by sequential reaction of two differing 1,2-disubstituted indoles with the anhydride. Further examples of asymmetric 7-azaphthalides with indoles and benzindoles have also been cited.⁸⁵ These color formers give red to purple images with clay and phenolic resin developers with good light stability.

Mixtures of 4- and 7-azaphthalides carrying a wide variety of heterocycles such as carbozoyl, pyrrolyl, acridinyl, phenothiazinyl, thianaphthenyl, and thienyl as well as indolyl of the general formulas **19** and **20** have also been described.⁸⁶ Table 1 illustrates the variety of hues available with such compounds.

4-Azaphthalides carrying indolyl and indolizinyll substituents have been shown⁶⁵ to produce blue color formers, while the combination of indoles



(19)



(20)

Table 1. Hues Available with Mixtures of 4- and 7-Azaphthalides Carrying Various Heterocycles

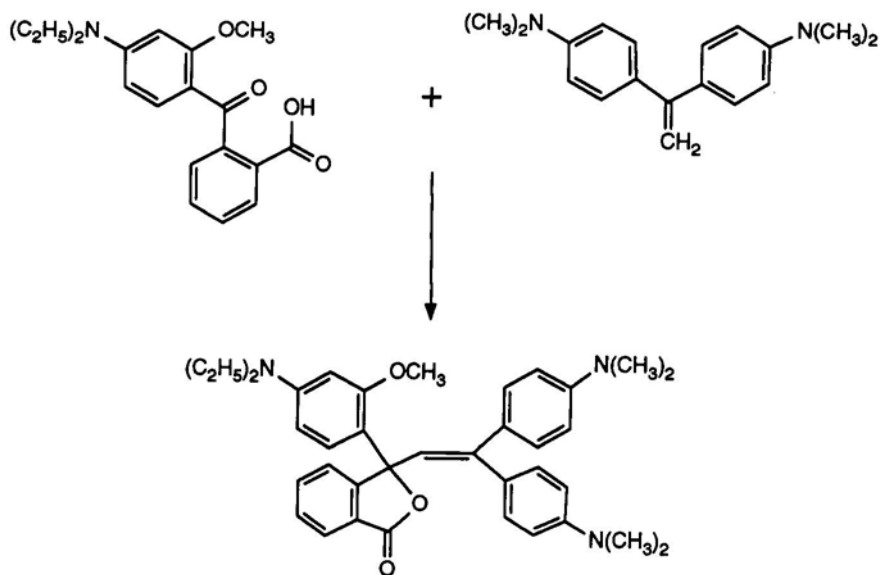
A	B	Color on clay
3-Indolyl	3-Carbazol yl	Purple
3-Carbazol yl	3-Carbazol yl	Blue
2-Pyrrolyl	3-Carbazolyl	Purple
2-Acridinyl	3-Carbazolyl	Green
2-Acridinyl	2-Thianaphthenyl	Orange-red
3-Indolyl	3-Phenothiazinyl	Red
3-Indolyl	2-Thien yl	Red

with imidazo[1,2-*a*]pyridines results in red images with clay developers.⁶⁶ Pyrazine-2,3-dicarboxylic acid anhydride has been found⁸⁵ to react analogously, producing red color formers on sequential reaction with benzindoles and pyrroles, while indoles and indolizines produce blue derivatives.⁶⁵ Finally, quinoxaline-2,3-dicarboxylic acid anhydride has frequently been reacted with indoles, and the intermediate ketoacid then condensed with benzindoles,⁸² indolizines,⁶⁵ and imidazo[1,2-*a*]pyridines to produce red, blue-black, and orange color formers, respectively.

4.6. ALKENYL SUBSTITUTED PHTHALIDES

4.6.1. 3-Ethylenyl Phthalides

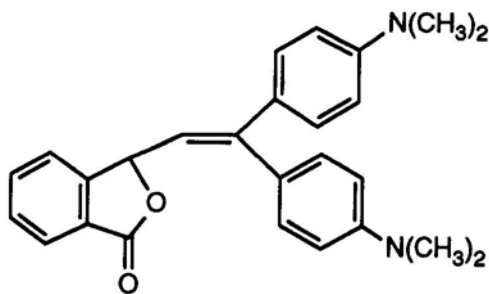
Introduction of an ethylene bridge between the *meso*-carbon atom and one of the diaminophenyl groups of a triarylmethane-type phthalide results in a considerable bathochromic shift, thus producing color formers exhibiting absorption in the near infrared region of the electromagnetic spectrum.



Scheme 9

The preparation of such compounds was first described in 1975 in a patent⁸⁷ encompassing a vast number of derivatives. Scheme 9 exemplifies the synthesis.

Condensation of the benzophenone with the diarylaminoethylene takes place in acetic anhydride and in the original report 3-indolylaryl-aminoethylenes were also described. In the meantime, a considerable number of variations have been reported, including the use of phenylaryl-aminoethylenes and also their synthesis from acetophenones and Grignard reagents.⁸⁸ The use of diarylamino benzophenonecarboxylic acids⁸⁹ and also 3-carbazolylphenyl analogues⁹⁰ have been described.

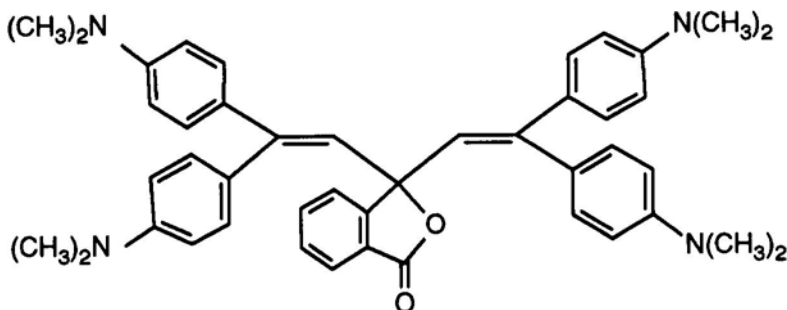


(21)

Reaction of 2-formylbenzoic acids with 1',1-bisdialkylaminoethylenes in acetic anhydride has been found⁹¹ to yield phthalides such as **21**. These color formers are claimed to yield blue to green images, but have also been described⁹² as intermediates for the preparation of divinyl phthalides by a route identical to that described in Scheme 3, for which they are probably of more significance. (See Section 4.6.2.)

4.6.2. 3,3-Bisethylenyl Phthalides

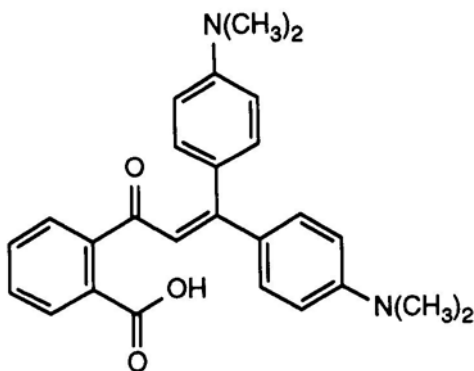
Introduction of two diaminophenylethylene moieties at the 3-position of the phthalide ring naturally also produces color formers exhibiting infrared absorption. As in Section 4.6.1, the first report⁹³ encompasses a vast number of compounds such as **22** which was prepared by treating phthalic anhydride with 2 mol of 1,1-bisdimethylaminophenylethylene in acetic anhydride.



(22)

Reaction proceeds via the intermediate keto acid, but, in practice, a one-pot procedure was employed. Substitution of the phthalide ring by chlorine or bromine atoms and replacement of the dimethylaminophenyl groups by tetrahydroquinoline or a 4-pyrrolidinylphenyl residue has been reported⁹⁴ to yield color formers possessing high resistance to heat, moisture, and light. Similar effects have also been claimed^{95,96} for compounds in which one dialkylamino group was replaced by an alkoxy substituent, the preparation of the required diarylethylenes from acetophenones and Grignard reagents also being described. Tetrachlorophthalic anhydride has

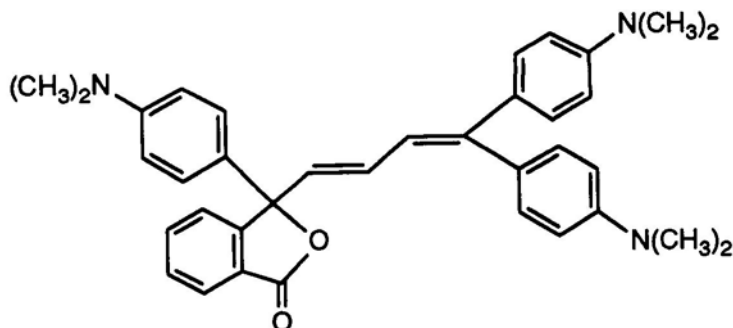
also been reacted⁹⁷ with 1-(3-dimethylaminophenyl)-1-(4-dimethylaminophenyl)ethylene to give a color former exhibiting a remarkably high absorption (935 nm), in combination with a phenolic resin developer. As mentioned in Section 4.6.1, phthalides such as **21** are useful intermediates since oxidation, for example with 3-nitrobenzenesulfonic acid, yields benzophenones (**23**), which may then be reacted with a second different ethylene to give asymmetric bisethylenyl phthalides.⁹⁸



Finally, bisindolythylenes have also been reacted with tetrahalophthalic anhydrides to yield color formers showing absorption in the near infrared.⁹⁹ The chief advantage over the diarylethylenes is the availability of the starting materials. The bisindolythylenes may be prepared *in situ* by reaction of an indole with acetyl chloride and then converted directly to the phthalide without isolation.

4.6.3. 3-Butadienyl Phthalides

One further example of this principle of extended conjugation to produce infrared-absorbing color formers is the introduction of the butadienyl group at the 3-position of the phthalide ring.¹⁰⁰ Thus, 2-(4-dimethylaminobenzoyl)benzoic acid was reacted with 1,1-bis(4-dimethylaminophenyl)buta-1,3-diene in acetic anhydride to yield the phthalide **24**. This idea, however, does not appear to have been greatly exploited, probably due to the fact that the ring-closed phthalides themselves are colored. The only other report¹⁰¹ to date describes analogues of **24** in which



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the 3-dimethylaminophenyl group is replaced by heterocycles such as carbazole, indole, tetrahydroquinoline, or julolidine.

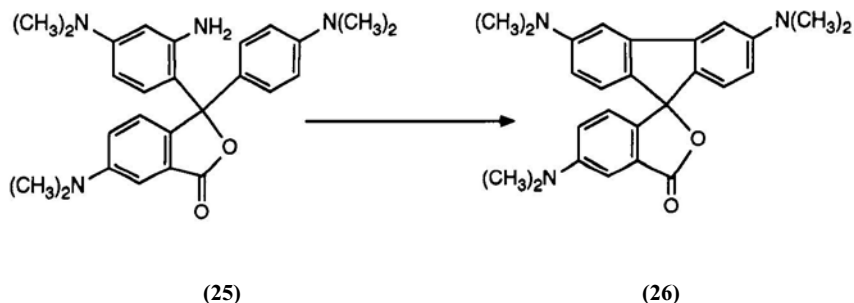
4.7. BRIDGED PHTHALIDES

4.7.1. Spirofluorene Phthalides

Fusion of the two arylamino groups of a triarylmethane phthalide color former results in the formation of spirofluorene phthalides. Due to the increased planarity of this system, a bathochromic shift results leading also to color formers showing infrared absorption when developed. This was first exemplified in 1983¹⁰² by preparation of phthalide **26** as shown in Scheme 10.

The phthalide **25**, obtainable by condensation of 4,4'-bisdimethylaminobenzophenone-2-carboxylic acid with 3-dimethylaminoacetanilide and subsequent hydrolysis, was diazotized in sulfuric acid and the resultant diazonium salt treated with copper powder to yield **26**. However, better yields are reportedly obtained by carrying out ring closure of the diazonium salt in phosphoric acid.¹⁰³ A further synthetic route has also been described in which phthalides undergo intramolecular cyclization in the presence of aluminum chloride and urea.^{104,105} Thus, Crystal Violet lactone (**2**) has been directly converted into phthalide **26**.¹⁰⁶

Despite the fact that the first patent application¹⁰² also claimed preparation and use of azaphthalides, such compounds never, in fact, appear

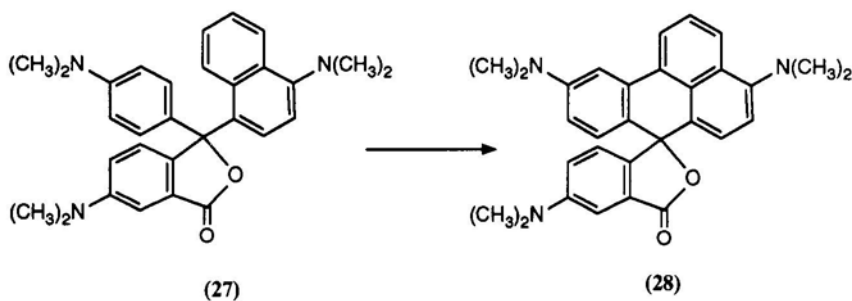


Scheme 10

to have been synthesized, and the only variations on the basic structure reported to date concern differing substituents on the amino groups. Thus, for example, alkoxyalkylamino and phenoxyalkylamino substituted analogues of **26** are claimed to possess superior stability toward heat after development,¹⁰⁷ but further-reaching structural variations have not been reported.

4.7.2. Spirobenzanthracene Phthalides

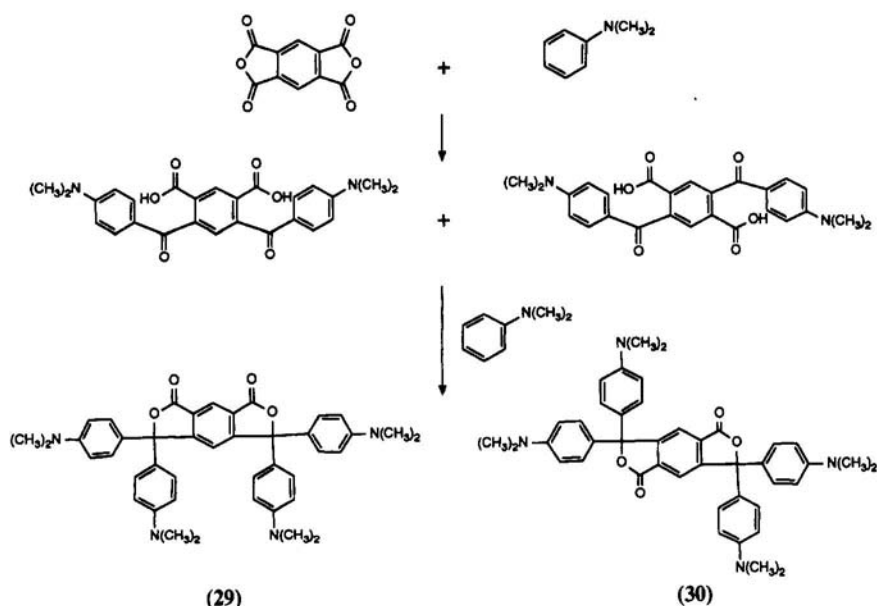
One further example of this principle of bridging the aryl groups of a triarylmethane phthalide was reported in 1986.¹⁰⁸ Thus, treatment of phthalide **27** with aluminum chloride results in the formation of the spirobenzanthracene **28** as shown in Scheme 11. These color formers also exhibit absorption in the near infrared spectral region, but no further reports of such compounds have since been published.



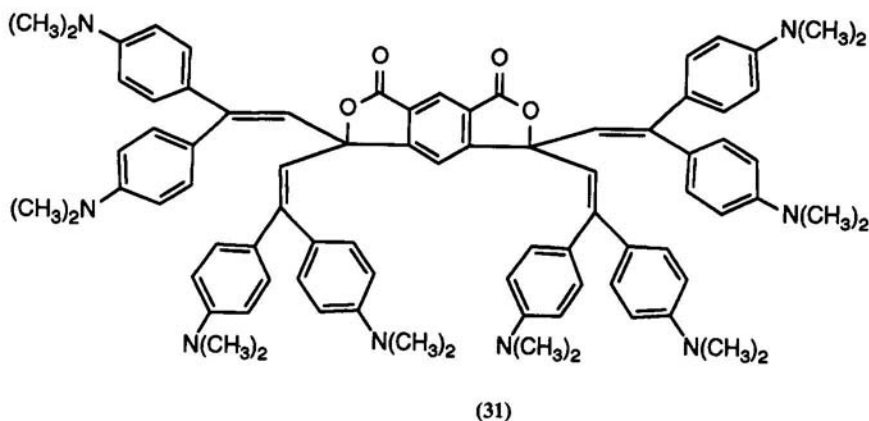
Scheme 11

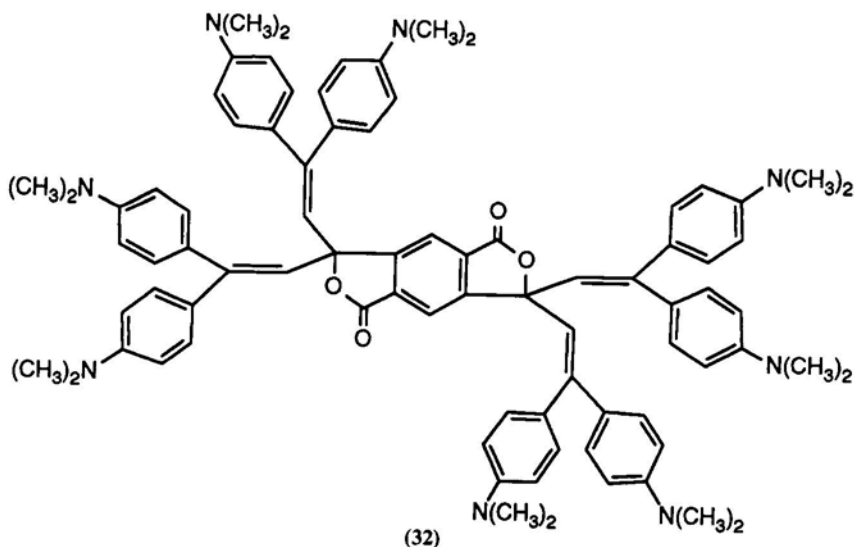
4.8. BISPTHALIDES

In analogy to the original preparation of Malachite Green lactone, pyromellitic anhydride has also been reacted with *N,N*-dimethylaniline in a zinc chloride melt to yield mixtures of the bisphthalides **29** and **30**.¹⁰⁹ However, far superior yields were obtained if reaction was carried out in two steps, as described in Scheme 12. The initial condensation was carried out



Scheme 12

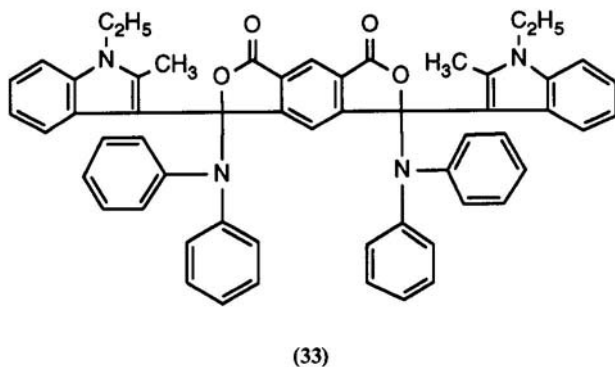


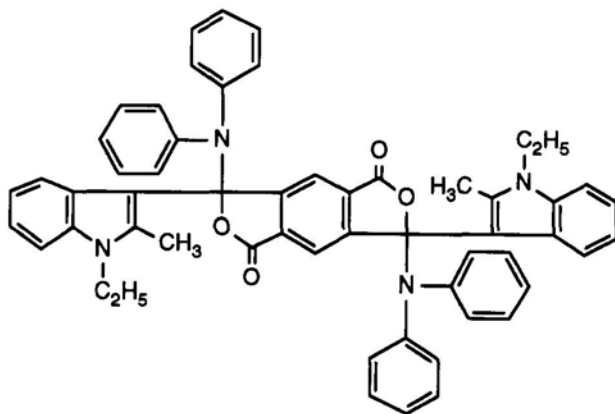


in the presence of aluminum chloride and the second in acetic anhydride leading to an approximately 1 : 1 mixture of isomers **29** and **30**. By utilizing different dialkylanilines in the second condensation, asymmetrically substituted compounds were also prepared. These color formers produce greenish-blue images on application to clay developers.

Reaction of pyromellitic anhydride with 1,1-bisdimethylaminophenylethylene has been shown¹¹⁰ to yield a mixture of the bisphthalides **31** and **32** which are infrared-absorbing color formers on clay.

Finally, 1-ethyl-2-methyl indole was reacted¹¹¹ with pyromellitic anhydride to give a mixture of keto acids, as in Scheme 12, which was then treated with diphenylamines to yield bisphthalides such as **33** and **34**. These color formers produce orange images on development, as also do those in which the indole residue is replaced by a 4-dialkylaminophenyl group.





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104. Yamamoto, Japanese Patent Application 61-022076 (Japanese Application 11.7.84) [*CA 105*, 105854].
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106. Yamamoto, European Patent Application 278,614 (Japanese Application 23.1.87) [*CA 110*, 775161].
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109. Burroughs, British Patent 1,017,695 (US. Application 31.8.61) [*CA 64*, 17607d].
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5

The Chemistry of Leuco Triarylmethanes

RAMAIAH MUTHYALA and XIANGFU LAN

5.1. INTRODUCTION

Di- or triarylmethane leuco dyes are those with electron-donating groups such as amino, or hydroxyl substituted at the *para* or less frequently at the *ortho* position of phenyl rings. To be of value as dye precursors, at least two amino groups or a combination of hydroxyl and amino groups are required. The amino groups can be primary, secondary, or tertiary. Additional substituents such as carboxylic acids, sulfonic acids, or halogens can also be present. The number, nature, and position of these substituents determine the hue or color of the dye and the type of application. For example, introduction of sulfonic acid group converts the basic dyes into acid dyes; a carboxylic group *ortho* to the phenolic hydroxyl group converts basic dyes into mordant dyes.

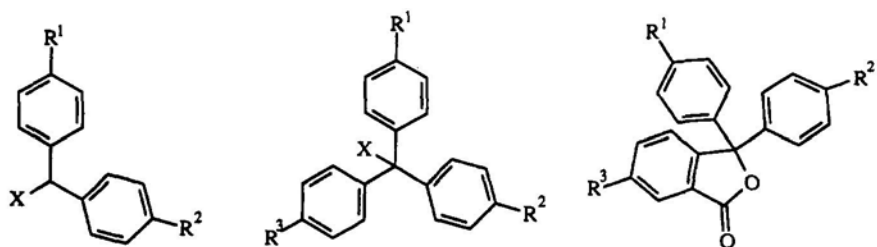
Arylmethane leuco dyes are converted into di- or triarylmethane dyes on oxidation. This class of dye precursors sometimes is referred to as leuco di- or triphenylmethane dyes, or di- or triphenylmethane leuco dyes. The use of the term di- or triarylmethane dyes can be misleading as the central carbon atom is a carbonium ion. Instead, the term di- and triarylmethine dye is recommended for this class as it correlates with the well-known polymethine dyes. Nevertheless, it has not been commonly used.

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Chemistry and Applications of Leuco Dyes, edited by Muthyala. Plenum Press, New York, 1997.

Triphenylmethane dyes show inferior lightfastness properties. They are, however, still one of the most important groups of synthetic dyes due to their brilliance, high tinctorial strength, and low cost. Several reviews have appeared on di- and triphenylmethane dyes.¹⁻⁵ However, the color-forming precursors — leuco dyes — have received less attention in the literature.

In general, the triarylmethane leuco skeleton can be represented by structures **1**–**4**. Traditional leuco di- and triphenylmethane dyes frequently include compounds of type **1** and **3**. The closely related compounds **2** and **4** are derived from **1** and **3**. Another closely related type is the lactone or phthalide **5** (see Chapter 4). In all of these leuco dyes, one or more of the phenyl rings can be replaced by a hetaryl ring or by a fused aromatic ring such as a naphthalene.



(1) $X=H$

(3) $X=H$

(5)

(2) $X=-NR_2, -SO_2R$

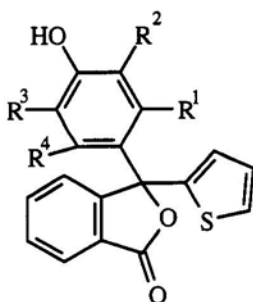
(4) $X=-OH, -OR, -NR_2, -CN, N\text{-Heterocycle}, -P(O)OR_2$

$R^1, R^2, R^3 = -NH_2, NR_2, -OH$

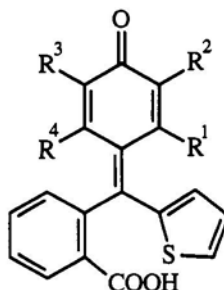
While the classical leuco dyes **1** or **3** form colors by hydride abstraction or oxidation, the leuco dyes **4** or **5** give colored substances on contact with an acid.

Triphenylmethane leuco dyes are far more important than the diphenylmethanes in terms of practical value. Use of triphenylmethane dyes for traditional applications of dyes is limited to dyeing wool, silk, leather, and polyacrylonitrile fibers. The largest portion of the annual production of this class of leuco dyes is consumed in the manufacturing of various copying papers.

The leuco triphenylmethanes are generally stable substances. However, IR studies have shown that in the solid state, some leuco dyes such as **6a–c**



(6)



(7)

(a) $R^1=OH, R^2-R^4=H$ (d) $R^1=R^4=H, R^2=R^3=OH$ (b) $R^1=R^4=OH, R^2=R^4=H$ (e) $R^1=R^2=H, R^3=R^4=OH$ (c) $R^1=R^2=OH, R^3=R^4=H$ (f) $R^1=R^3=OH, R^2=R^4=H$ (g) $R^1=R^2=R^4=H, R^3=OH$

exist as a mixture of phenol and the quinone carboxylic acids **7a–c**, whereas **6d–g** exist exclusively as lactone.⁶

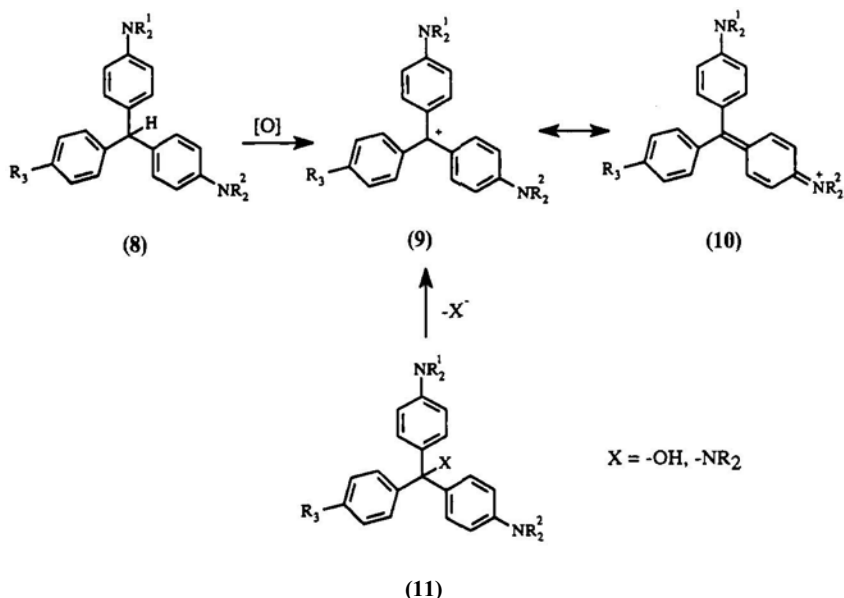
5.2. PROPERTIES OF DI- AND TRIARYLMETHANES

5.2.1. Color-Formation Reactions

Colorless triarylmethane leuco materials **8** can be converted to carbonium ion (**9**)-colored materials, either by hydride abstraction or by chemical or photooxidation. In addition, some leuco compounds such as **11** can be converted to colored materials by treatment with an acid. The latter case is similar to the chemistry observed for fluoran (see Chapter 6) or phthalide (see Chapter 4) leuco compounds (Scheme 1).

5.2.1.1. Via Oxidation

Direct oxidation of diphenylmethanes is of little practical value as color formers. In liquid sulfur dioxide, leuco diphenylmethane **12** (Scheme 2) undergoes hydride abstraction by triphenylcarbenium perchlorate at the benzylic amine position to form immonium ion⁷ **13**, whereas in acetonitrile

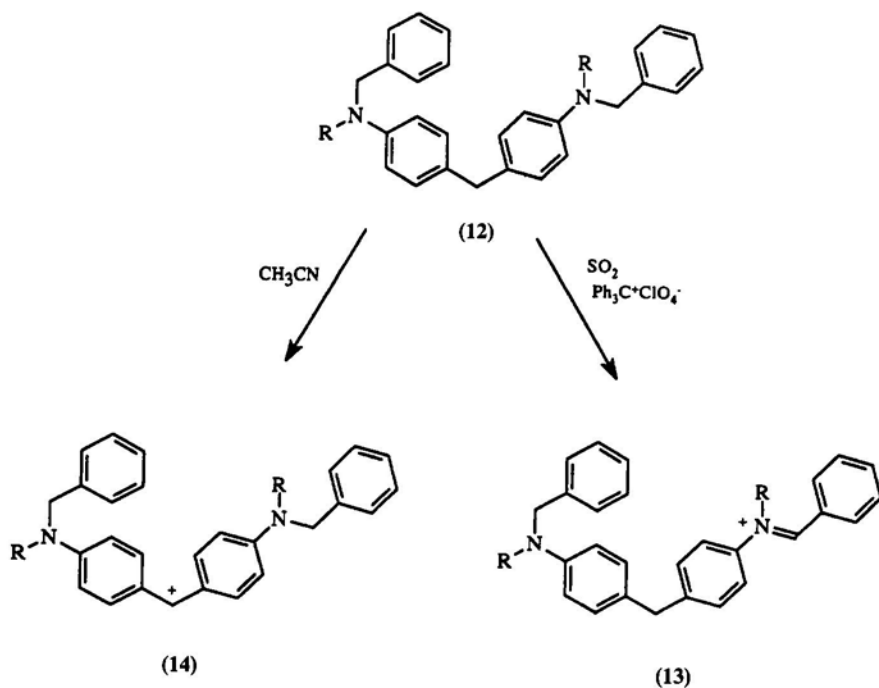


Scheme 1

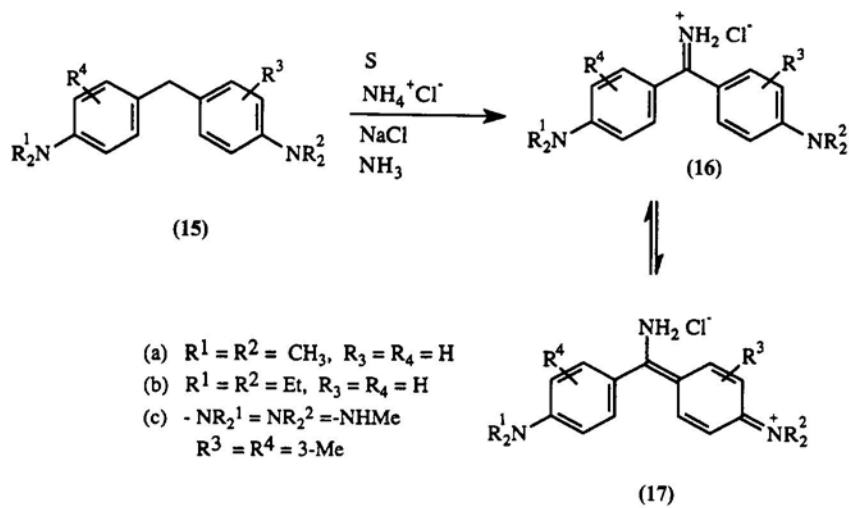
diphenylmethane dye **14** is formed. This example demonstrates the influence that the solvent can have directing effect on the hydride abstraction.

The practical route for oxidizing leuco diphenylmethanes **15** demands initial conversion to an imine salt **16**. The imine salt is obtained by heating a mixture of diphenylmethane, sulfur, ammonium chloride, and sodium chloride at 175°C in a current of ammonia; or by heating a mixture of diphenylmethane, urea, sulfamic acid, sulfur, and ammonia at 175°C (Scheme 3). Dyes **16** can be represented as the quinonoid resonance structure **17**. Dyes of this class, known as auramines, are all yellow, with the only commercial representative being auramine O **16a**. Due to its poor lightfastness and instability to hot acids and bases, its use has been restricted to dyeing and printing cotton, paper, silk, leather, and jute.

The chemical oxidants for triphenylmethanes are categorized into two groups: the strong oxidant group consists of PbO_2 , $Na_2Cr_2O_7/H^+$, and MnO_2 , while the mild oxidant group consists of oxygen or air, hydrogen peroxide, nitrobenzene, peroxomonosulfuric acid or its salts. Care must be taken in selecting the proper oxidant and the reaction conditions in order to prevent overoxidation. For example, oxidation of leuco Malachite Green with excess PbO_2 leads to decomposition products to quinoneimine and benzoic acid.



Scheme 2



Scheme 3

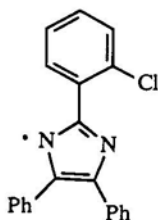
Although PbO_2 in HCl has been commonly used, an ecologically safer oxidant is MnO_2 in the presence of H_3PO_4 ⁸⁻¹¹ or HCl .^{9,12} In general, oxidation utilizing oxygen¹³ or hydrogen peroxide¹⁴ requires a catalyst, usually a metal complex. A catalytic amount of halo- or cyano-substituted benzoquinones,^{15,16} or nitro-substituted phenanthrenequinone^{13,17} has been used in conjunction with metal catalysts. The metal catalysts can be Mn, Fe, Cu, or Cr complexes of porpharines, tetraazac[14]annulene, phthalocyanine, or tetraazacyclodecane^{14,18} or molybdc acid, and VO_2^+ . The oxidation reaction is carried out in a solvent such as glacial acetic acid.¹⁸ For example, leuco Malachite Green in glacial acetic acid has been oxidized with Chloranil¹⁴ and air in the presence of an iron tetraaza[14]annulene complex at 50°C.

The kinetics for the oxidation of leuco bases using oxygen has been studied.¹⁹ The oxidation involves complex formation between the protonated leuco base and the peroxy radical formed by air oxidation of the solvent. Addition of a radical initiator (AIBN) facilitates the reaction, while radical inhibitors retard the dye formation. In addition, oxidation reactions employing 2,3-dichloro-5,6-dicyanoquinone have shown large isotope effects in acetonitrile.²⁰

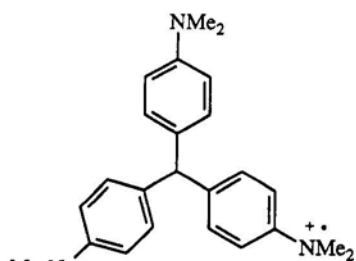
Anodic oxidation has been employed for water-soluble triphenylmethane dyes. It has been shown that the formation of dye is an irreversible two-electron oxidation process.²¹⁻²³ This method has been used for the oxidation of diamino triphenylmethane leuco compounds containing two to four sulfonic acid groups to obtain food-grade colored materials.²⁴

The photochemical oxidation of triphenylmethanes has been studied.²⁵⁻²⁸ In general, triarylmethanes are photooxidized to dyes under UV irradiation in the presence of hexaarylbisimidazoles.²⁹⁻³² The mechanism of the bisimidazole-sensitized photooxidation of leuco Crystal Violet has been studied.³³ The first step of the reaction involves an electron-exchange reaction between 2-(*o*-chlorophenyl)-4,5-diphenylimidazolyl radical **18** (generated from the corresponding dimer) and the leuco dye, forming a solvated electron and a radical cation^{26,34,35} **19**. Decay of the radical cation results in the formation of a dye cation **20** and a hydrogen atom. The presence of the radical cation **19**, the dye cation **20** as well as radical **21** has been shown by conventional and laser flash photolysis and by spin trap³⁶ experiments. Photolysis of leuco nitriles of Malachite Green and Crystal Violet suggests charge transfer between the electron-donor ($-\text{NMe}_2$) and electron-acceptor ($-\text{CN}$) groups.³⁷

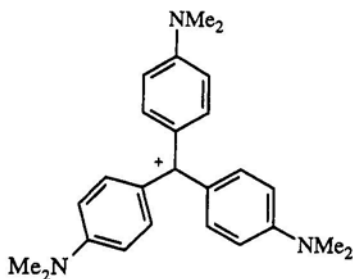
When a benzene solution of benzaldehyde and leuco Crystal Violet is irradiated in air, it undergoes an exceptionally fast photochemical reaction and the dye is formed in an excellent yield.³⁸



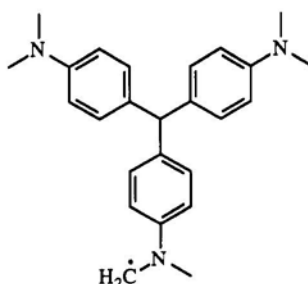
(18)



(19)



(20)



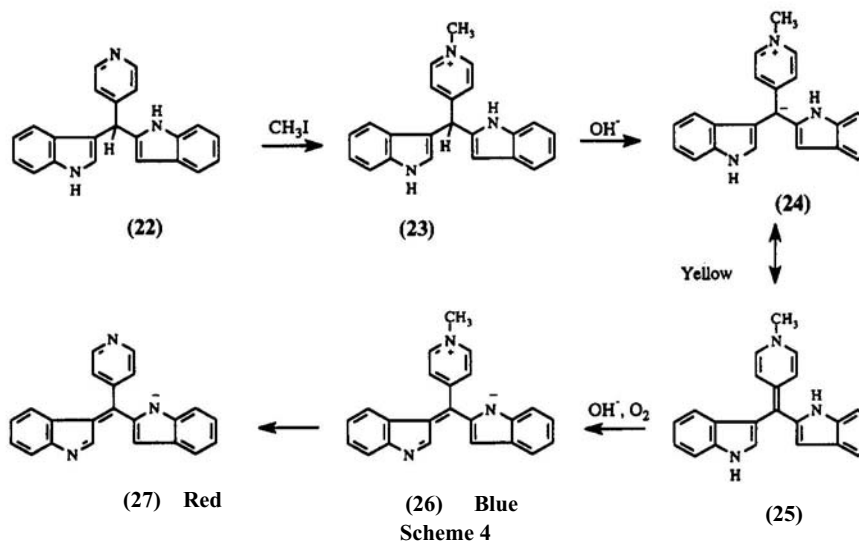
(21)

5.2.1.2. Action of Acids

The formation of colored materials from leuco bases such as **4** and **5** is accomplished by treatment with acids such as acid clay, bisphenol A, acetic acid, or silica gel.³⁹ For leuco base **4** the leaving group is hydroxy, alkoxy, or cyanide, or a nitrogen-containing heterocycle.

5.2.1.3. Alkylation of Triheteroarylmethanes

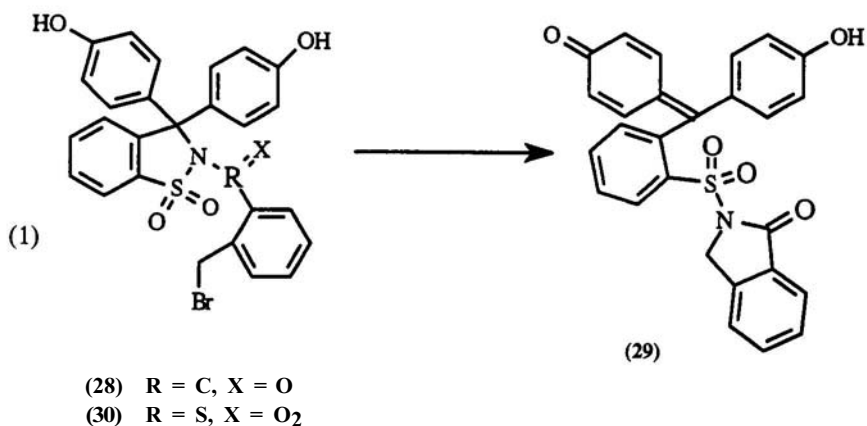
The formation of color from triheteroarylmethanes differs from the methodology employed for triphenylmethane leuco dyes⁴⁰ (Scheme 4). Dyes are initially formed by alkylation of the pyridyl nitrogen, followed by deprotonation at the central methine carbon. Thus, treatment of the colorless 3,3'-diindolyl-4-pyridylmethane **22** with excess methyl iodide produces colorless compound **23**. Subsequent treatment of **23** with hydroxide

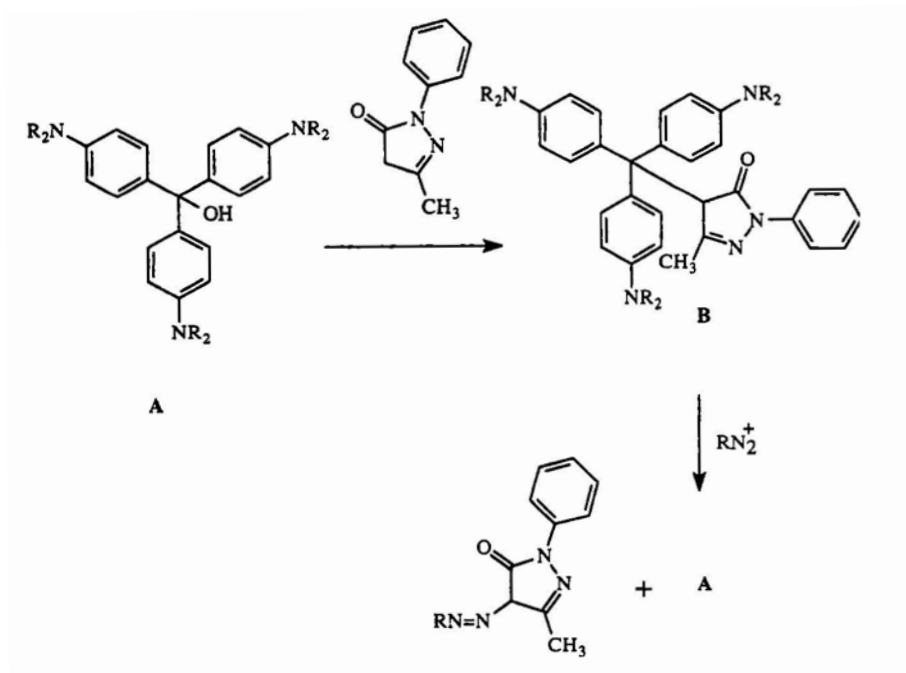


yields a yellow dye **24**, which undergoes rapid oxidation to give a blue dye **26** followed by slow dealkylation to yield the red dye **27**.

5.2.1.4. Miscellaneous

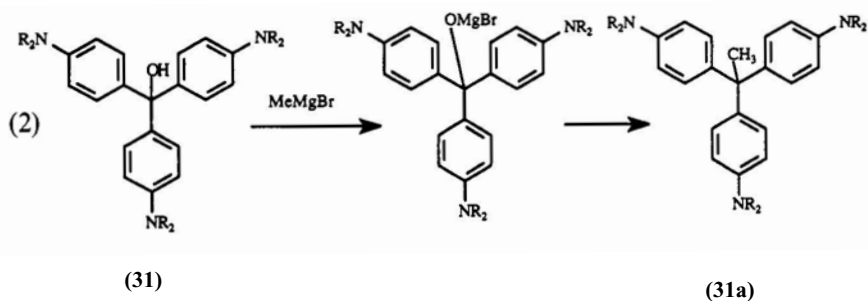
Some dyes can be formed from triphenylmethane leuco materials by simple thermolysis. For example, when **28** is heated an irreversible intramolecular alkylation reaction occurs to form the stable dye⁴¹ **29** (Eq. 1).





Scheme 5

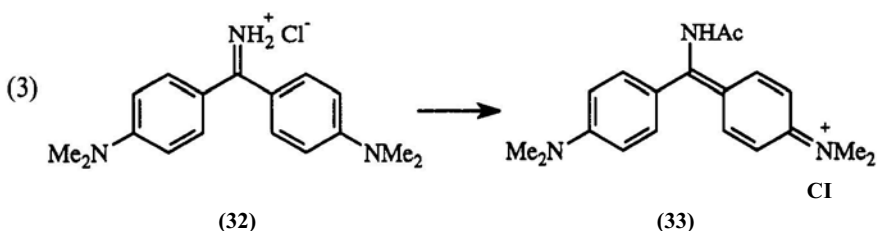
Besides the formation of colored compounds, leuco dyes can undergo other chemical reactions. For example, leuco bases can be sulfonated⁴² or nitrated.⁴³ Leuco dyes containing phenolic groups can be converted into phosphonate esters by treatment with $(\text{PhO})_3\text{P}$ or $(\text{PhO})_2\text{P}-\text{OH}$.⁴⁴ Triphenylmethanecarbinols react with phenylmethylpyrazoles to form C—C bond compounds of type **B** (Scheme 5). The carbinol can be regenerated on treatment with a diazonium salt. Furthermore, the addition of Grignard



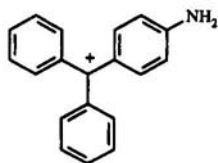
reagents to triphenylmethane carbinols forms **31A** via a Tseretvetinov reaction (Eq. 2). Triphenylmethane carbinol methyl ethers of **31** undergo similar reactions with Grignard reagents.⁴⁵

5.2.2. Effect of Substituents on Color

Like most dyes, substituents on di- and triphenylmethane dyes have a significant effect on the absorption spectra. Acetylation of the imino nitrogen of auramine O (**32**) results in shift to longer wavelength (Eq. 3). A

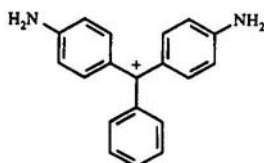


general rule for triphenylmethane dyes is that the greater the fraction of positive charge that is on the auxochromes, the longer the wavelength of absorption. A bathochromic shift can be achieved by introduction of electron-donating groups. For example, 4-aminotriphenylmethane **34** is orange yellow, 4,4'-diaminotriphenylmethane **35** is red-violet, and 4,4',4''-triaminotriphenylmethane **36** is bluish red. Alkyl groups on nitrogen result in further bathochromic shift. Phenylation of amine nitrogen leads to even



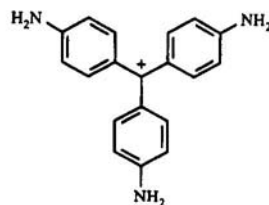
orange Yellow

(34)



Red-Violet

(35)



Bluish red

(36)

greater bathochromic shifts. Replacement of the aromatic amino group with phenolic substituents results in hypochromic shifts. However, the sodium salt of phenolic dyes have similar absorption to the amine-substituted derivatives.

Steric effects play an important role in the absorption of triphenylmethane dyes. Introduction of *ortho* substituents on the phenyl rings results in bathochromic shifts. This is due to the twisting of the phenyl rings resulting in a greater localized positive charge on the auxochromic nitrogens.⁴⁶ For example, tris(4-diethylaminophenyl)methane gives a purple dye on oxidation, while tris(4-diethylamino-2-methylphenyl)methane gives a blue material.

5.3. SYNTHESIS

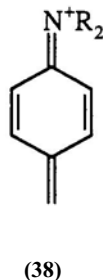
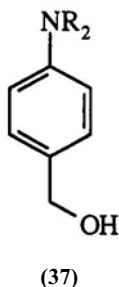
5.3.1. Diphenylmethanes

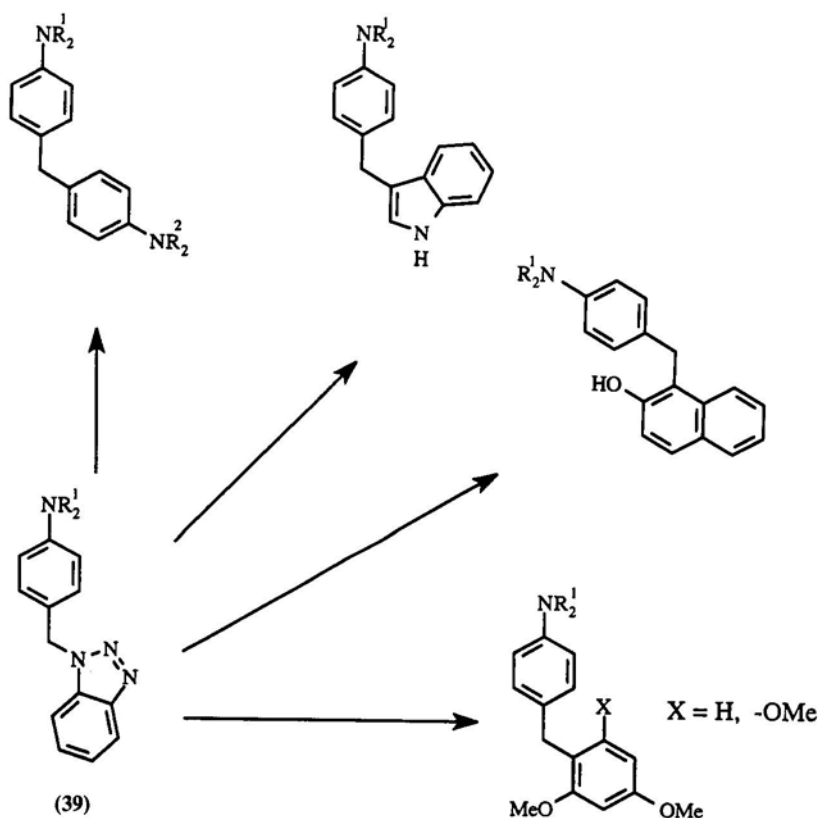
Diphenylmethanes that have two identical phenyl groups are synthesized by the condensation of formaldehyde or its equivalent with an arylamine in the presence of concentrated hydrochloric acid.⁴⁷⁻⁵¹ However, it is usually difficult to stop the reaction at the diphenylmethane stage.

Magnesium phenolates react with triethylorthoformate regiospecifically at the *ortho* position of the phenoxy group (normally phenols give alkyl ethers) giving diarylmethanes. This reaction is complex and the product composition depends on the phenol and the reaction conditions.⁵²

Reaction of 4-hydroxymethylaniline **37** with a variety of arylamines in the presence of an acid catalyst gives both symmetrical and unsymmetrical diphenylmethanes.⁵³⁻⁵⁵ This reaction proceeds via intermediate **38**.

Aniline or *N,N*-dialkylanilines are readily alkylated by 1-(hydroxymethyl)benzotriazole to give 4-(benzotriazol-1-yl-methyl)anilines **39** (Scheme 6). Subsequent displacement of the benzotriazole group with



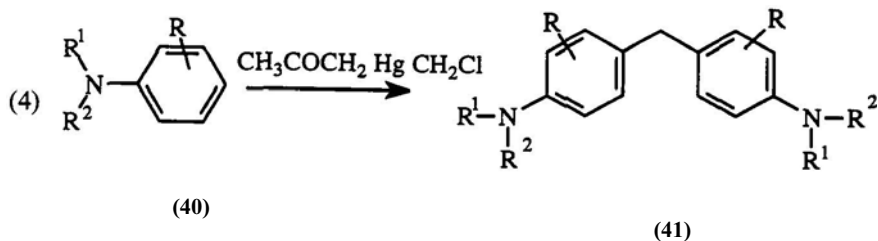


Scheme 6

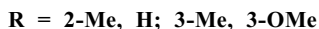
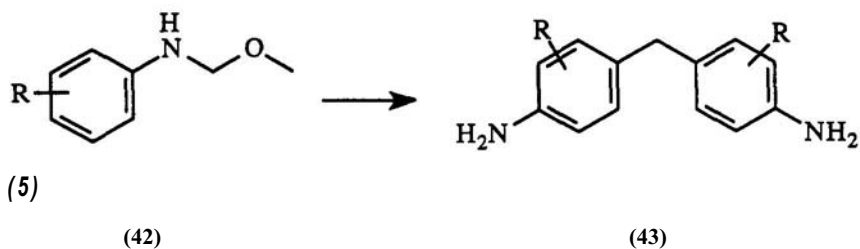
arylamines or *N,N*-dialkylamines gives either symmetrical or unsymmetrical 4,4'-methylene-bis-*N,N*-dialkylphenylamines.^{56,57}

A general experimental procedure⁵⁷ for a diarylmethane leuco compound via a benzotriazole: To a stirred solution of the corresponding (benzotriazol-1-yl-methyl)aniline (5 mmol) in methanol (30 ml) under reflux was added a solution of the appropriate aromatic compound (5 mmol) and concentrated hydrochloric acid (1 ml) in water (30 ml). The resulting mixture was heated under reflux followed by the addition of aqueous KOH (1 M, 50 ml). The product was isolated by filtration or by extraction with ether, and further purified by recrystallization or by column chromatography.

Oxidation of dimethylaniline with organometallic compounds such as osmiumcarbonyl,⁵⁸ or palladium(II) compounds⁵⁹ or *t*-butylperesters⁶⁰ give bis(4-*N,N*-dimethylaminophenyl)methanes. The reaction of monohalogeno-alkyl mercurials with aromatic amines **40** in a molar ratio of 1:4 gives bis(4-aminophenyl)alkanes⁶¹ **41** (Eq. 4).



Treatment of *N,O*-acetals **42** in which the *para* position is unsubstituted, with a twofold excess of the corresponding amine HCl in boiling 50% aqueous methanol gives rise to the bis(4-aminoaryl)methane derivative.⁶² **43**. This method is suitable only for 4-*N,N'*-unsubstituted diarylamines (Eq. 5).



Reduction of benzophenones with $\text{FeCl}_2/\text{NaB}(\text{Et})_3\text{H}^{63}$ or LiAlH_4^{64} or with $\text{NaBH}_4/\text{CH}_3\text{SO}_3\text{H}^{65}$ gives bis-phenylmethanes in low yields. Alternatively, bidentate or monodentate aromatic mercury salts reduce thioketones to diarylmethanes.⁶⁶

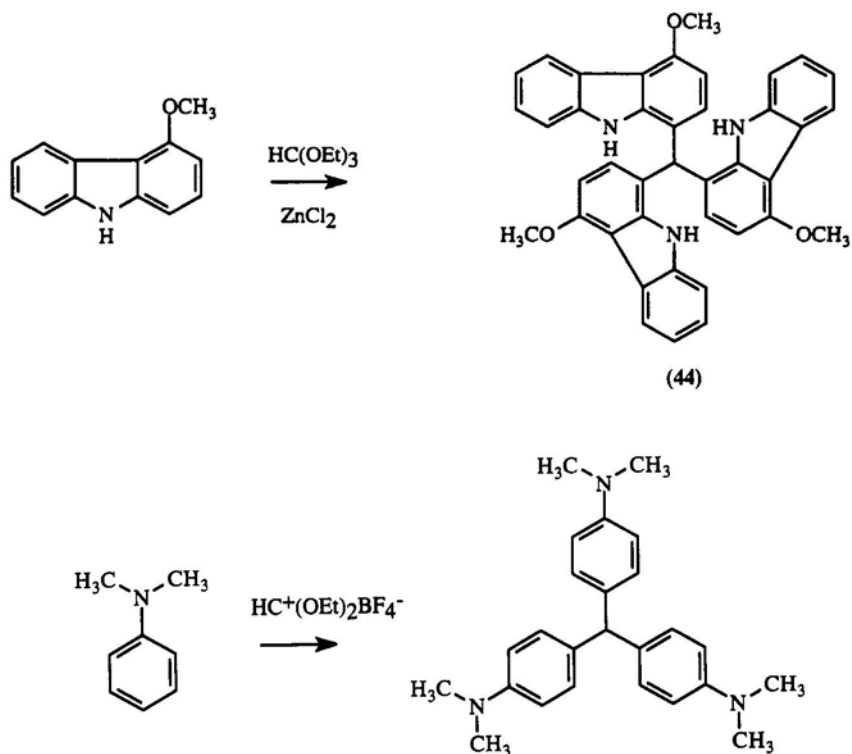
Leuco diarylmethane compounds which have received a good deal of attention are the leuco auramines. Reaction of Michler's hydrol with a

suitable amine, hydrazine, or sulfonamide gives auramine derivatives. These derivatives have low volatility with increased solubility in oil and show good stability in the leuco state.¹⁶

5.3.2. Triphenylmethanes and Carbinol Bases

5.3.2.1. Via One-Carbon Synthons

Triethyl orthoformate or chloroform can react with arene nucleophiles to give triphenylmethanes with three identical aryl groups.^{5,52,67} In addition, dialkylarylamines, when treated with dialkoxycarbenium tetrafluoroborates under thermodynamic conditions or with triethyl orthoformate/zinc chloride in ether under anhydrous conditions, give triarylmethanes.⁶⁸ For example, 4-methoxycarbazole and triethyl orthoformate in the presence of acid catalyst give **44** in 66% yield⁶⁹ (Scheme 7). In general, phenolic or

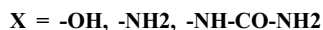
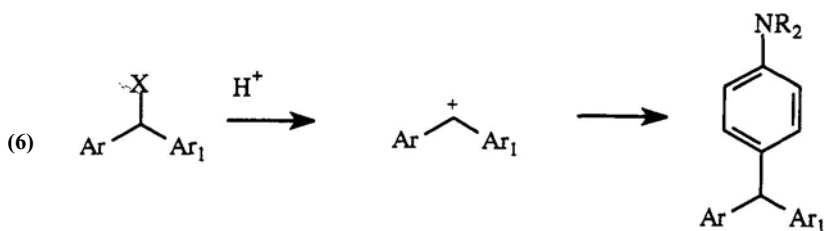


Scheme 7

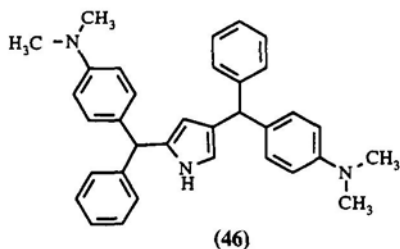
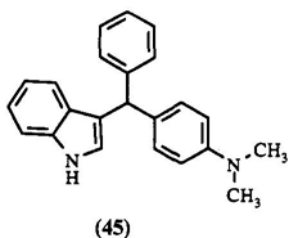
arylamino aldehydes or their orthoesters yield a mixture of di- and triaryl-methane compounds. This synthetic method is best used for preparing triarylmethanes.

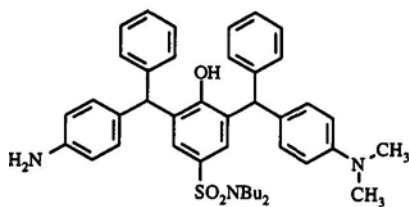
5.3.2.2. Via Benzhydrols

The benzhydrols are obtained by reacting an aromatic aldehyde with an arylamine or by oxidation⁷⁰ of a diphenylmethane derivative with PbO_2 or MnO_2 . The benzhydrol intermediate is then treated with an arene nucleophile in the presence of acid catalysts such as aluminum chloride,⁷¹ concentrated hydrochloric acid,⁵⁵ phosphoric acid,⁷² or sulfuric acid⁷³ to give triphenylmethane leuco dyes.^{74,75} Under these conditions, the benzhydrol is protonated at the hydroxy group on the central carbon atom. A carbocation is formed by the loss of water (Eq. 6). Electrophilic substitution then occurs on the *meso* carbon atom yielding the desired product. Amino,⁷⁵

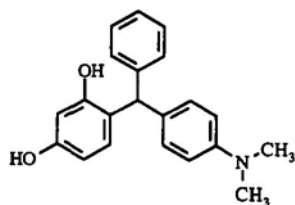


ureido, or bisureido groups^{15,73,76} have also served as leaving groups. The compounds **45–50** are prepared by this method. The aromatic nucleophiles

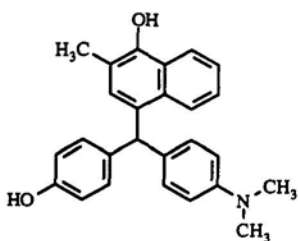




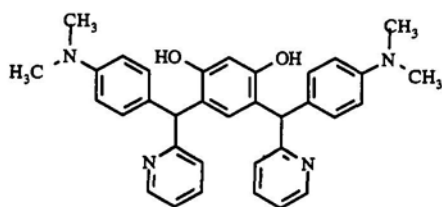
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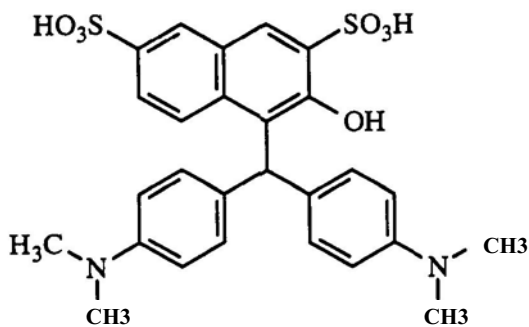


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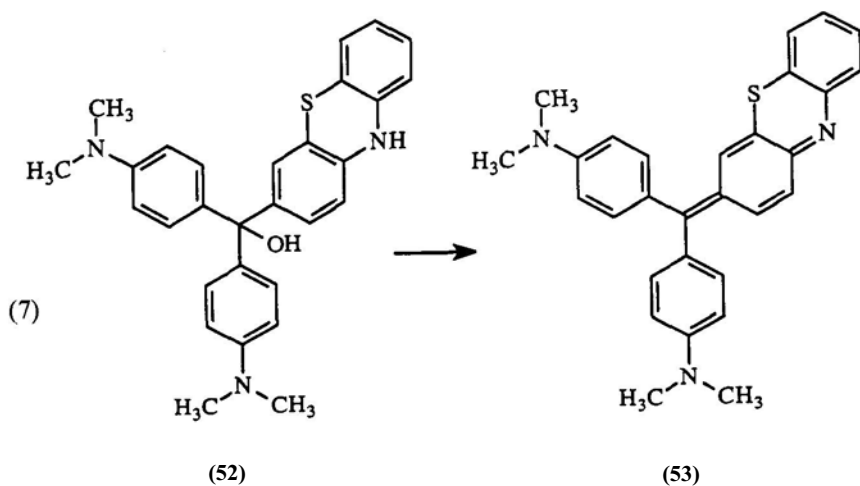


(50)

usually contain electron-donating groups, but comparatively deactivated aromatic nucleophiles such as sulfonated arylamines and naphthalenes can also be used. For example, 4,4'-bis(dimethylamino)benzhydrol (Michler's hydrol) reacts with β -naphthyl-3,6-disulfonic acids to give leuco compound 51.

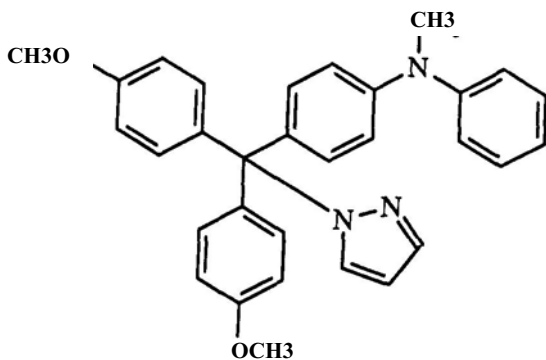


(51)



Carbinol bases are obtained by treating cationic triphenylmethine dyes with alkali.⁷⁷ However, not all carbinol bases are stable. For example, **52** readily eliminates water to form the neutral quinonimide⁴⁵ **53** (Eq. 7).

Hydroxy leuco bases can be converted into the corresponding amino leuco bases by allowing the leuco compound to react with a secondary amine in the presence of acetic acid.⁷⁸ Examples, **54**, of amine bases utilized in this manner are imidazole, 1,2,4-triazine, aryl amine, and cyclohexyl amine.

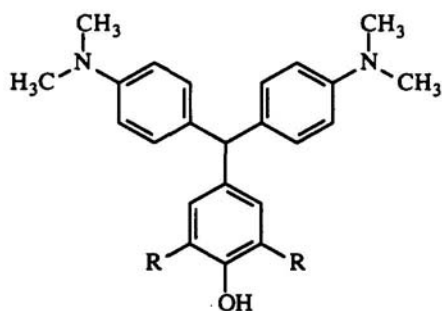


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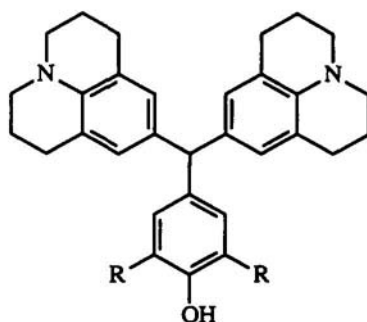
*Experimental Procedure*⁷⁹ for 3-[α -(4-dimethylaminophenyl)benzyl]indole (45). To a solution of 4-*N,N*-dimethylaminobenzhydrol (0.45 g, 2 mmol) in MeOH (25 ml) under reflux, was added a solution of indole and concentrated hydrochloric acid (0.8 ml) in water (25 ml). The mixture was heated under reflux for 90 min, followed by the addition of KOH solution (5%, 30ml). After the reaction was allowed to cool, the product was isolated by filtration (0.63 g, 97%).

5.3.2.3. Via Aromatic Aldehydes

The reaction of an aromatic aldehyde with an aromatic nucleophile containing hydroxy or amino groups gives products with at least two identical phenyl groups⁷⁹⁻⁸³ e.g., 55, 56. Use of two different nucleophiles generally results in lower yield.

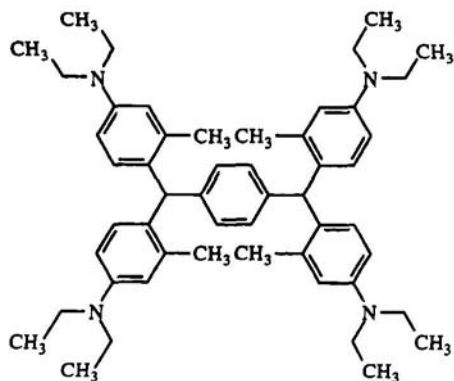


(55) a) R = -OCH₃
b) R = -^tBu

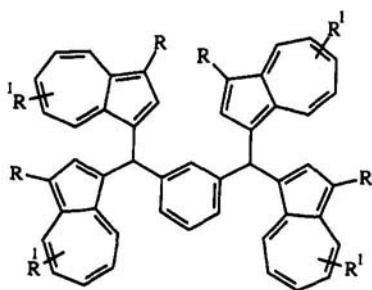


(56) a) R = -OCH₃
b) R = -^tBu

Benzene and naphthalene compounds can be formylated under Vilsmier conditions. The formyl compounds, with or without isolating, can be condensed with amino arenes to give leuco compounds. In this reaction, the benzhydrol intermediate is not isolated.^{21,79,84-86} The reaction is generally carried out in an alcohol solvent such as isopropanol, butanol, or pentanol and an acid catalyst such as hydrochloric acid, sulfuric acid, or methanesulfonic acid.⁸⁷ Acetic acid can also be used both as catalyst and as the solvent. Urea sometimes is added as catalyst.^{84,88} Terephthalaldehyde reacts with *N,N*-diethyl-3-methylaniline⁸⁹ and substituted azulenes to give a bis-triphenylmethane²¹ 57 and 58, respectively.



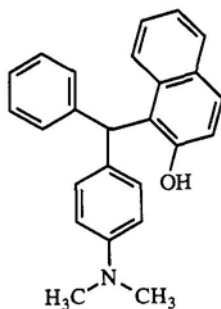
(57)



(58)

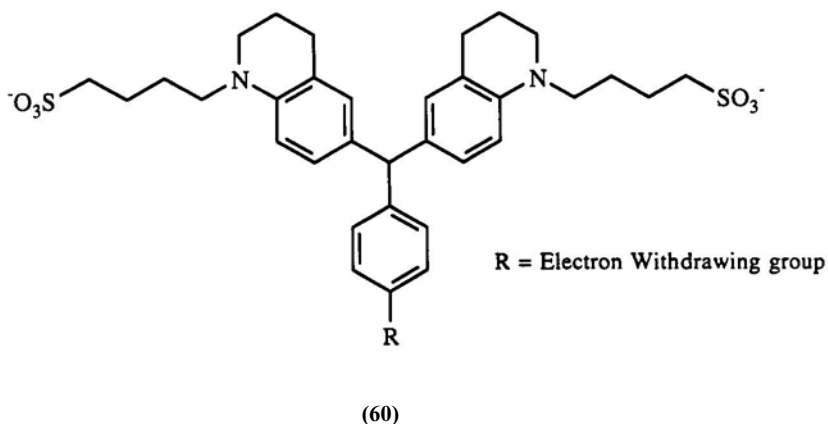
*Experimental Procedure*⁷⁹ for 4-bis(4-dimethylaminophenyl)methyl-2,6-dimethoxyphenol (**55a**). A mixture of syringaldehyde (5.46 g, 30 mmol), *N,N*-dimethylaniline (7.26 g, 60 mmol), urea (2.7 g), and concentrated sulfuric acid (4.41 g) in isopropanol (100ml) was heated at 90°C under a nitrogen atmosphere for 24h. The reaction was cooled to room temperature and 40ml of water added followed by 50% NaOH until alkaline. The mixture was filtered and the residue washed with 200ml of cold water. The solid was recrystallized from ethanol and yielded 12.0g (97%), mp 136–138°C.

Two different nucleophiles can be used but lower yields of the triaryl methane leuco dyes containing three different rings are obtained. For

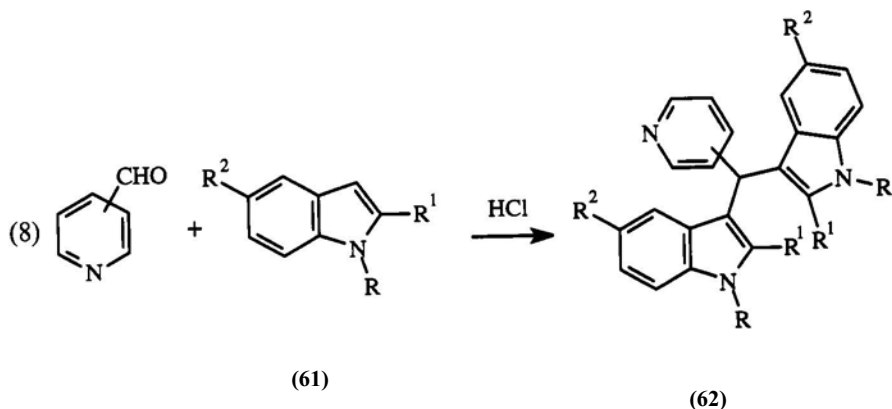


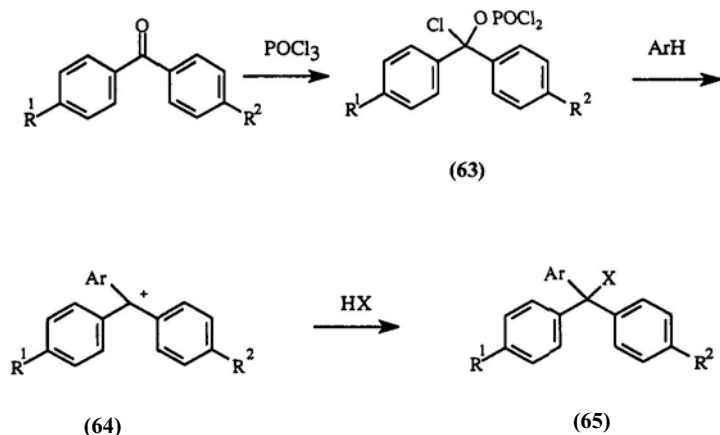
(59)

example, a mixture of benzaldehyde, 2-naphthol, and *N,N*-dimethylaniline gives only 24% yield of the triaryl methane **59**. Water-soluble triaryl methanes **60** are also prepared from 4-cyanobenzaldehyde and tetrahydroquinolines.⁹⁰



In place of aromatic aldehyde, a hetaryl aldehyde such as 2-pyridinecarboxaldehyde can also be used.⁸⁴ If a hetaryl aldehyde such as 4-pyridinecarboxaldehyde and a hetaryl nucleophile such as indole **61** are used, a trihetaryl methane of type **62** is formed⁹¹ (Eq. 8). The reaction normally occurs at the 3-position of indole. However, when the 3-position is substituted, the reaction occurs at the 2-position. Use of two different indoles





	R ₁	R ₂	Ar	X	Ref.
a)	MeO-	MeO-		OH	83,134
b)	EtO-	EtO-		OEt	80,114
c)	H	Ph-N-Ph		OMe	81
d)	H	H		OH OMe	82
e)	MeO-	MeO-			84

Scheme 8

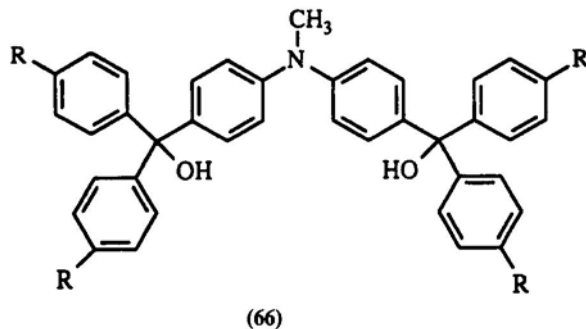
affords the unsymmetrical analogues in low yields, as expected. This product is usually accompanied by the formation of the two symmetrical analogues.

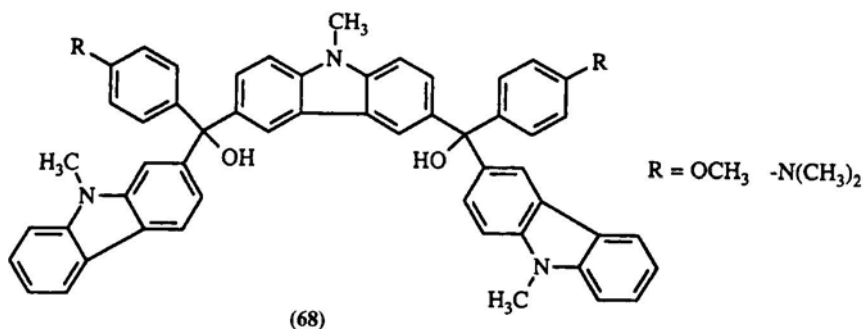
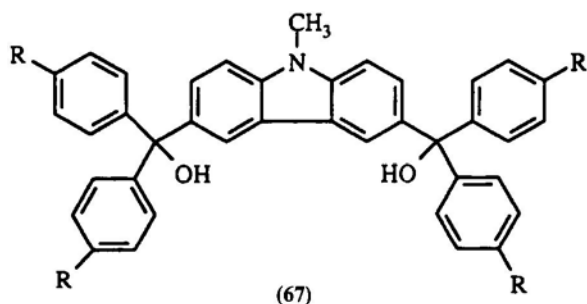
Unlike triarylmethane dyes, comparatively little work has been done with diaryl heteryl-, and aryl diheteryl methane compounds. Analogous to triarylmethanes, triheterylmethane dyes are also prepared using POCl₃ and a ketone. The intermediate leuco compounds (similar to **65**, see Scheme 8) are not isolated⁴⁰ in the case of triheterylmethane leuco dyes.

*Experimental Procedure*⁹¹ for 3,3'-diindolyl-4-pyridylmethane (**62**, $R^1 = R^2 = R^3 = H$). Indole (2.34g, 0.02mol) and 4-pyridinecarboxaldehyde (1.07 g, 0.01 mol) are dissolved in ethanol (100 ml). Concentrated HCl (20ml) was added and the mixture allowed to stand at 25°C for 2h. Water (300ml) was added giving a fine white precipitate. The milky suspension was neutralized with concentrated NH_4OH , yielding a light yellow precipitate. After filtration and drying, **62** was obtained (2.87 g, 89%), mp 156–158°C.

5.3.2.4. Via Aromatic Ketones

Formation of leuco compounds from ketones is generally a two-step process. The reaction of aromatic ketone with an arene nucleophile is normally carried out in the presence of excess $POCl_3$ with P_2O_5 , $ZnCl_2$, or $SOCl_2$. $POCl_3$ serves as solvent and also as water acceptor. Usually dyes are formed directly in this reaction. Without isolation, they are treated with a base such as $NaOH$,⁷⁷ $NaOMe$,^{92,93} $NaOEt$,⁹⁴ or a heterocycle such as imidazole⁷⁸ to give the carbinol base, or the nitrogen substituent analogue, respectively. Benzophenone and substituted benzophenones containing an alkoxy or amino substituent are often used. Anilines, substituted anilines, and heterocycles such as *N*-ethylcarbazole,⁹² indole, 1,2-dimethylindole,⁴⁰ tetrahydroquinolines, and quinoxaline^{93,95} have been used as nucleophiles. This reaction proceeds via intermediate **63** (Scheme 8). Replacement of the chlorine atom by the aromatic nucleophile gives the dye cation **64** followed by quenching with a base to give leuco compounds. For example, *N*-methyldiphenylamine reacts with *N*-methylcarbazole in this way to give the bis-triarylmethane leuco compound⁶⁸ (e.g., **65a**) and other similar compounds^{96–98} **66–68**.

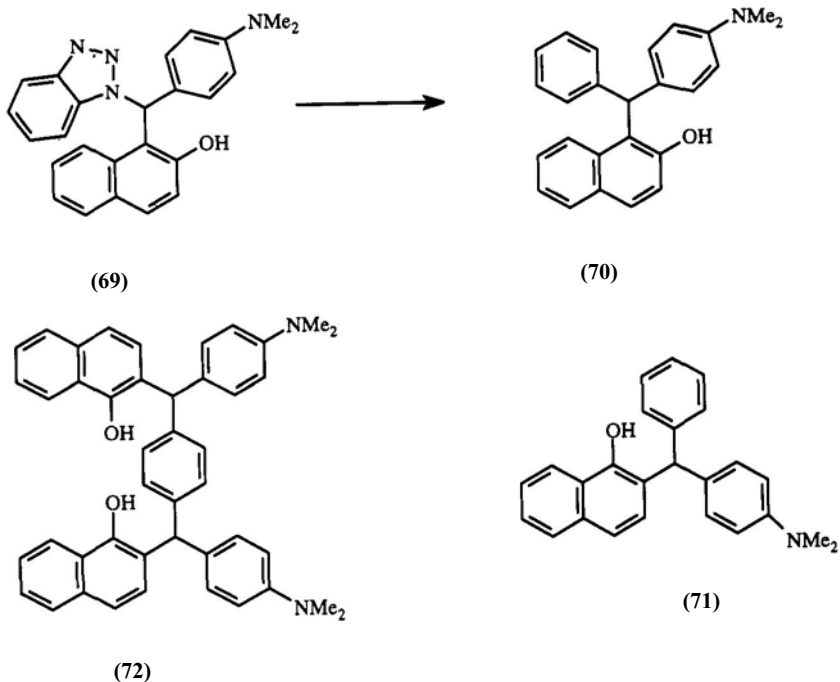




*Experimental Procedure*⁹⁶ for 4,4'-diethoxy-4''-[N-methyl-N-(4-cyanophenyl)amino]-ethoxytriphenylmethane (**65b**). 14.1 g of P_2O_5 added at room temperature to a mixture of 4,4'-diethoxybenzophenone (13.5 g, 0.05 mol) and 4-cyanodiphenylamine (10.4 g, 0.05 mol) in 38.2 g of POCl_3 . The mixture was stirred at 40°C for 20h, poured into 500ml of ice water, and stirred at room temperature for about 10–15h until the dyestuff separated out as crystals. The crystals were isolated by filtration and, washed with water and dried in vacuum at 40°C to give 24.1 g (97%) dark red-violet crystals mp $69\text{--}75^\circ\text{C}$. 19.9g (0.04mol) of this dye in 200ml of EtOH was slowly added dropwise to 120ml of 1 M NaOEt solution at room temperature. The mixture was stirred at room temperature for 20 h, and filtered. The solvent was removed and the oily residue was stirred with 500ml of water and then cooled to $10\text{--}15^\circ\text{C}$. The reaction mixture was filtered and the residue was dried in vacuum at room temperature to give 18.5g (91%) of colorless crystal mp $48\text{--}55^\circ\text{C}$.

5.3.2.5. Benzotriazole Method

Use of benzotriazole in the preparation of diphenylmethanes and triphenylmethanes has been reviewed.⁹⁹ Benzotriazole is condensed with an aldehyde and then allowed to react with naphthols to form a diphenylmethane benzotriazole derivative such as **69** (Scheme 9). The benzotriazole moiety in **69** is displaced by a Grignard reagent to give triphenylmethanes.^{79,100} This method allows for the preparation of triarylmethanes which contain three different aromatic rings. Compounds **70–72** are prepared by this method.

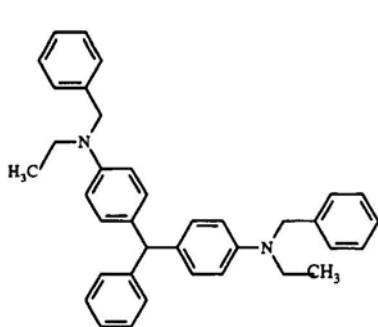


Scheme 9

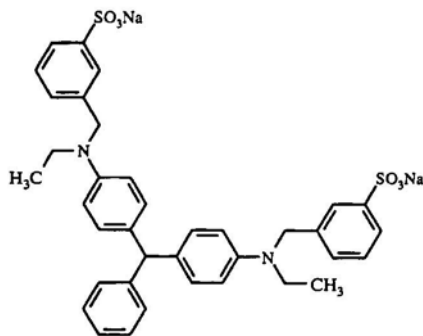
*Experimental Procedure*⁷⁹ for 1,4-bis(4-dimethylaminophenyl) (1-hydroxynaphthalen-2-yl)methylbenzene (**72**). To a solution of 1,4-bis(benzotriazol-1-yl) (1-hydroxynaphthalen-2-yl)benzene (3.74 g, 6 mmol) in dry THF (240ml) at -78°C was added a solution of 4-dimethylaminophenylmagnesium bromide (60mmol, 1.0M in THF, 60ml). The mixture was allowed to warm to room temperature and stirred overnight. It was then poured into water (100ml), acidified with HCl (2 N), and extracted with Et₂O (4 $\times$ 100ml). The ether extracts were dried (MgSO₄) and concentrated to give solid. The solid was purified by column chromatography with gradient eluent (hexane/CH₂Cl₂ 4:1, then CH₂Cl₂) to give product (1.42 g, 38%) as glassy solid.

5.3.2.6. Miscellaneous Methods

Sulfonated triphenylmethane leuco dye **73** is prepared⁴² by sulfonating the leuco dye **74** with 20–30% of the theoretical amount of 20 – 65% oleum at 30 – 50°C. The dye, derived from leuco base **73** by oxidation, is used in the



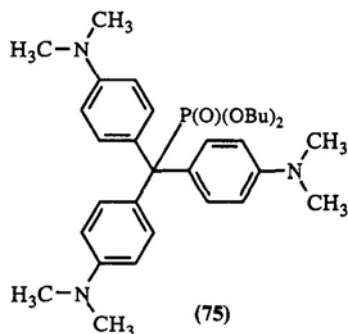
(74)



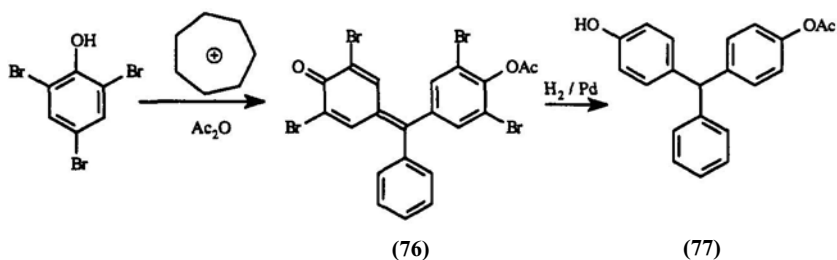
(73)

production of black-and-white photographic film. Crystal Violet reacts with tributyl phosphite in chloroform to give Crystal Violet dibutyl phosphonate¹⁰¹ **75** which is claimed to have improved light stability.

The leuco forms of Basic Fuchsin, Crystal Violet, and Malachite Green are prepared by reduction of the corresponding dyes using Na₂S/H₂SO₄ at pH 8.2–9.6. Acid Fuchsine, Brilliant Green, and Malachite Green have been reduced by using H₂S gas bubbled in ammonium hydroxide solution.¹⁰²

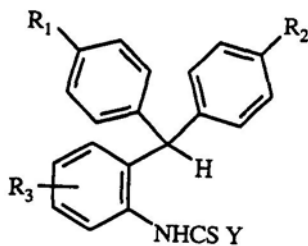


The reaction of 2,4,6-trihalophenols with tropylium perchlorates in the presence of triethylamine gives phenolate dye (Scheme 10) followed by acetylation to give dye **76** from which the leuco compounds **77** can be prepared¹⁰³ by catalytic reduction using Pd-C/H₂.

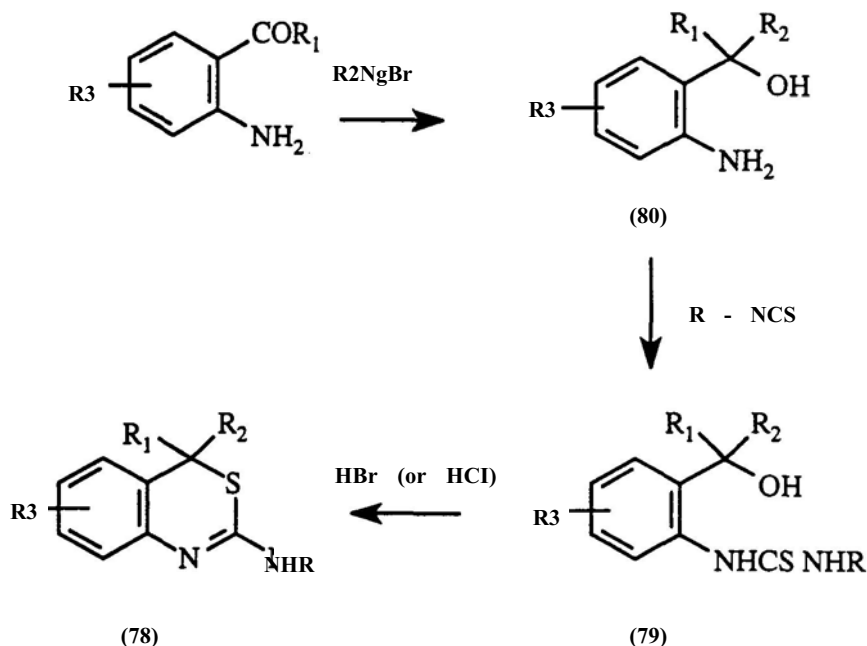


Scheme 10

4*H*-3,1-Benzothiazine derivatives **78** are synthesized according to Scheme 11. This process is carried out by reacting an *o*-amino- α,α -disubstituted benzyl alcohol **80** to yield a thioisocyanate followed by ring closure



(81)



Scheme 11

of the resulting *o*-thiourido- α,α -disubstituted benzyl alcohol **79** by means of hydrogen bromide or hydrogen chloride. Alternatively, they can also be prepared by the oxidation of thioamide derivatives of triarylmethanes **81** using manganese dioxide or lead dioxide.¹⁰⁴ Dyes prepared from these leuco compounds are resistant to light.

5.4. APPLICATIONS

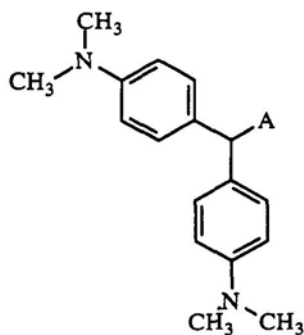
Triphenylmethanes are used mainly for nontextile purposes. Almost all of the leuco bases of triphenylmethane dyes are used in the color-forming applications, e.g., in novel types of colorless copying papers. Other applications include pressure-sensitive heat-sensitive materials, high-speed photo duplicating copying papers, light-sensitive papers, ultrasonic recording papers, electrothermic heat-sensitive recording papers, inks, crayons, type-written ribbons, and photoimaging systems. Many of these applications generally involve microencapsulation of the leuco dye in one layer, an electron acceptor or acid in another layer. When they are brought into

contact either by pressure, heat, or light, electron-transfer reactions occur and a color image is generated. Images are generated by a variety of techniques. For example, a leuco dye and an acid solution can be dispersed and printed on a rayon unwoven cloth. When a pattern is used to partially cover the sheet and then a solvent such as ethanol is sprayed on the surface, a copy of the pattern on a colored background is generated.¹⁰⁵

5.4.1. Pressure-Sensitive Recording Materials

Pressure-sensitive recording materials are obtained by dissolving a triphenylmethane leuco dye in a solvent composed of paraffin oils. The microcapsules are formed from a water-soluble¹⁰⁶ or water-dispersible material.^{107,108} Leuco dyes dissolved in sunflower oil are microencapsulated in a solution containing a melamine-HCHO precondensate and coated on the back side of a paper sheet. Contact of the microcapsule-coated sheet with an acid-coated receptor sheet allows the color formation to occur.

A clay mineral and/or its acid-treated products^{109,110} are used as color developers. A diphenylmethane derivative of structure **82** has been micro-



A = N-Heterocycle, -NHNH-, -O-, -OR, NHR

(82)

capsulated and used as pressure-sensitive recording material¹¹¹ to give light-, water-, and plasticizer-resistant colors.¹¹² Normal triphenylmethane derivatives are good solvents for the triphenylmethane color formers.¹¹³

5.4.2. Thermal Recording Materials

Thermal recording materials consist of a heat-sensitive layer made by dispersing a leuco triphenylmethane dye and a phenol in a binder where the

two reactive materials are kept apart by a water- or nonpolar solvent-soluble polymer surface film. The phenolic materials are generally solids at room temperature. At the thermographic copying temperature the phenolic materials become liquid or gas and this allows for the reaction of the leuco dyes to produce a colored image.¹¹⁴

5.4.3. Photosensitive Recording Materials

Triphenylmethane leuco dyes are used for photographic materials. The photographic system requires a polymer binder such as acrylic acid-methyl methacrylate copolymer¹¹⁵ or a copolymer of isophthalic and terephthalic acids¹¹⁶; a sensitizer such as 4-(4-n-amyloxyphenyl)-2,6-bis(3-ethylphenyl)-thiapyrylium perchlorate,¹¹⁷ a photo initiator such as hexaarylbisimidazole,¹¹⁸ and phenyl tribromomethyl sulfone, cycloalkane such as 1,2,3,4,5-pentabromo-6-chlorocyclohexane,¹¹⁹ or 3-benzylidene-9-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline.¹²⁰

The redox system consists of pyrene or 9,10-phenanthrene quinone as oxidant and an alkyl ester of 3,3',3''-nitrilopropionic acid as reductant.¹²¹ This system deactivates oxidation by bisimidazole when irradiated at 380–550nm, since the quinone is reduced to hydroquinone and thus stabilizing the previously generated dye image.^{122,123}

5.4.4. Miscellaneous Applications

Besides their major use in pressure-sensitive, thermal, and photographic recording materials, triphenylmethane leuco dyes are extensively used in biological and analytical applications. They are used for detection of hydrogen peroxide in medical diagnostic kits (e.g., glucose determination, by glucose oxidase), in biotechnology process control,^{124,125} in analysis of biological fluids, and in wastewater treatment plants.¹²⁶

The color formation property is also used for detection of carboxylic acids,¹⁰² anionic surfactants by spectrophotometric method¹²⁷ in the 0–1500 ppm range. This procedure is suitable for automation. Triphenylmethane carbinol bases and leuco cyanides have found use in making photoresponsive polymers. UV irradiation of polymers containing triphenylmethane leuco bases produces intensely colored cations through photodissociation followed by recombination of the cation with counterions on heating. This property can be used to produce reversible photomechanical transfer material.¹²⁸ An acrylamide gel with a triphenylmethane nitrile shows reversible photostimulated dilation effect.¹²⁹ When irradiated, dye cation is formed allowing creation of osmotic pressure differentials, causing swelling of gel. When in the dark, the gel deswells to its initial size due to the re-formation of the leuco nitrile.

Hexa(hydroxyethyl)pararosaniline nitrile has been used in a chemical radiochromic dosimeter.¹³⁰ Ferricyanide oxidation of leuco Crystal Violet to Crystal Violet dye finds use in detection of various heavy metals¹³¹ at trace quantities. Oxidation of leuco triphenylmethanes by chloramine-T is catalyzed by iodide and therefore is used for detection of iodide.¹³² On the other hand, the inhibition of the catalytic effect of iodide by some ions can be used for determining traces of Ag(I), Hg(II), Pd(II). In addition, the triphenylmethane leuco dyes, phenolphthalein or phenol red are used extensively as indicators in calorimetric and titrimetric determinations.

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6

The Chemistry of Fluoran Leuco Dyes

YOSHIHIRO HATANO

6.1. INTRODUCTION

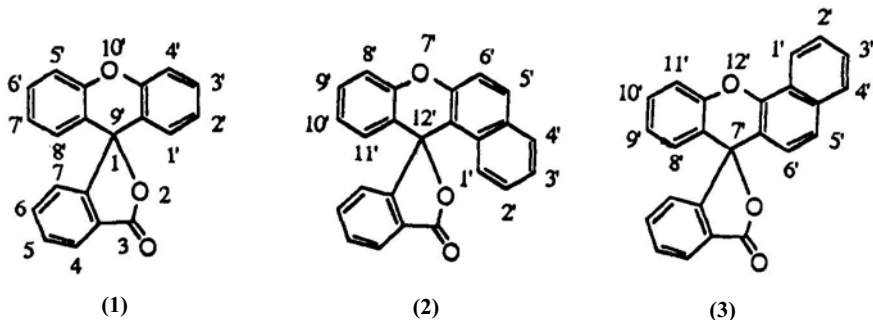
In our information-oriented society, computer and facsimile are being widely used as a means for transmitting information. Carbonless copying papers and thermosensitive recording papers, which utilize a color-formation reaction between leuco dyes and acidic compounds, have won high regard as recording papers used with these office machines. The leuco dyes are colorless or nearly colorless solids, but develop colors on contact with acidic compounds or electron-accepting compounds. Among various classes of leuco dyes, fluoran compounds have the remarkable feature of giving a wide variety of colors depending on their substituent(s). In particular, fluoran compounds are very important in their ability to yield singly black color which is hardly attained by the other classes of leuco dyes.

Fluoran (**1**) is the commonly used name for the spiro[isobenzofuran-1,9'-xanthen]-3-one. Benzo[*a*]fluoran (**2**) has the benzene ring fused to the 1- and 2-positions of the xanthene moiety. Fusion at the 3- and 4-positions gives benzo[*c*]fluoran (**3**). Numbering of the atoms is employed as shown in **1–3**.

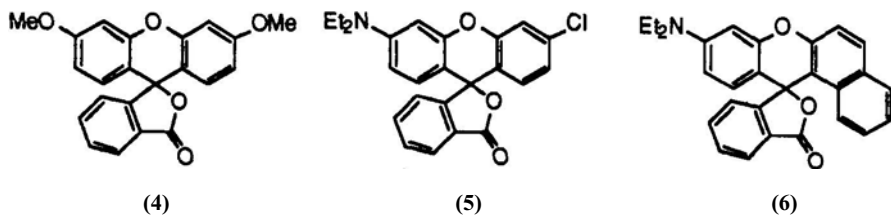
Fluoran compound used as leuco dye needs to have substituent(s) on the xanthene moiety to develop color, though fluoran **1** itself is prepared as a by-product in the synthesis of phenolphthalein from phenol and phthalic anhydride.

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Chemistry and Applications of Leuco Dyes, edited by Muthyala. Plenum Press, New York, 1997.



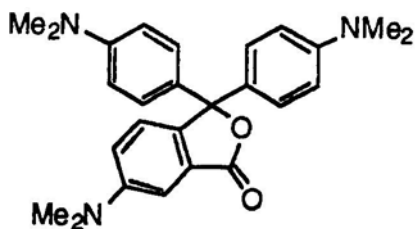
Fluoran compounds developing colors are not new, having been well known since early times. For example, the *Beilstein Handbook of Organic Chemistry*, XIX describes many fluoran compounds developing colors from yellow to red. These include 3',6'-dimethoxyfluoran (**4**; yellow), 3'-chloro-6'-diethylaminofluoran (**5**; vermilion), and 9'-diethylaminobenzo[*a*]fluoran (**6**; red).



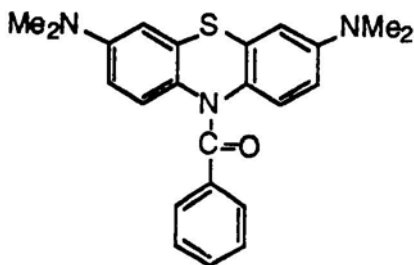
Fluoran compounds generally lack color stability, and therefore had lost their value as dyestuff for textile finishing. It is, however, very interesting that the old-fashioned fluoran compounds have come around as leuco dyes for use in the new applications.

In 1954, the National Cash Register Company first marketed carbonless copying paper—NCR paper¹—using Crystal Violet lactone (**7**)¹ and benzoyl leuco Methylene Blue (**8**)² as leuco dyes to make blue images.

In order to develop new leuco dyes, a great number of studies subsequently concentrated on fluoran compounds particularly in Japan, where there were high demands for carbonless copying papers developing black color. It was, however, not until the 1970s that black developing fluoran compounds became available. The first stage was, therefore, to produce orange or yellowish red developing fluorans such as 2'-chloro-

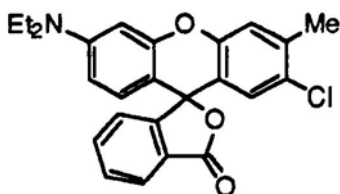


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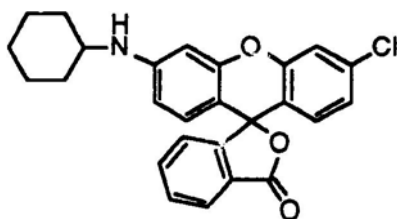


(8)

6'-diethylamino-3'-methylfluoran (9),³ 3'-chloro-6'-cyclohexylaminofluoran (10),⁴ etc., to make mixed black color together with 7.



(9)

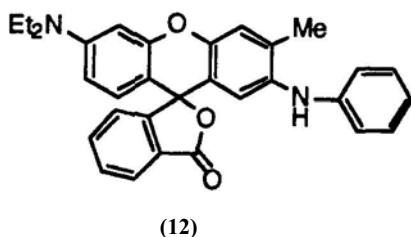
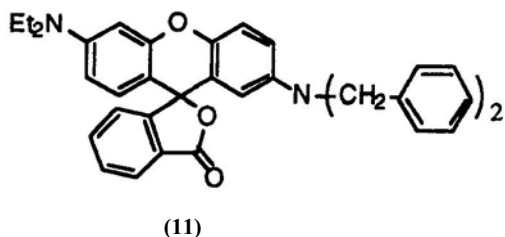


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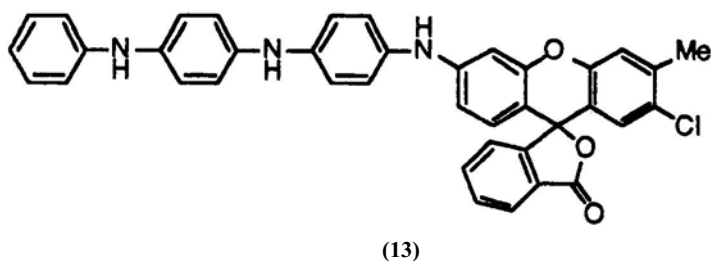
The mixed black was, however, not very practical, because 7 is very high in saturation resulting in an unbalanced color tone.

It was then that a very important invention that cannot be exaggerated for the development of fluoran chemistry was made, namely, the invention of 2'-dibenzylamino-6'-diethylaminofluoran (**11**)⁵ developing dark green color. Regarding dye chemistry, it was very surprising that such a small molecule as fluoran **11** develops green color. Fluoran **11** gives practical black color together with a red developing leuco dye, which mixed black color is even today used for carbonless copying papers employed inorganic coreactants.

A singly black developing leuco dye was ultimately realized by the invention of 2'-anilino-6'-diethylamino-3'-methylfluoran (**12**).⁶ Fluoran **12** skillfully utilizes the steric hindrance of a methyl group at 3'-position to develop black color (see discussion below). Practically all black developing fluoran compounds marketed today are derivatives of **12**, though each has an individual characteristic, especially for use in thermosensitive recording papers.



In addition, fluoran compounds such as 6'-[4-(4-anilinoanilino)anilino]-2'-chloro-3'-methylfluoran (**13**)⁷ giving images readable by near-infrared rays have also been developed for POS (points of sales) labels that are recently being watched with keen interest.



This chapter describes the properties and syntheses of fluoran compounds, and their applications as well.

6.2. PROPERTIES OF FLUORAN COMPOUNDS

6.2.1. Color-Formation Reaction

Colorless or nearly colorless fluoran compounds having appropriate substituent(s) react with acidic compounds to open their lactone rings resulting in extension of the conjugated double bond system, enabling color formation. Lactone ring opening can be determined very easily by the disappearance of lactone absorption around 1760 cm^{-1} in the infrared spectrum. For example, a solution of fluoran **12** in toluene develops black color on the addition of an acidic compound (Figure 6.1).

A perspective view of **12** is shown in Figure 6.2. X-ray structure analysis⁸ on the fluoran shows that the xanthene moiety is slightly bent

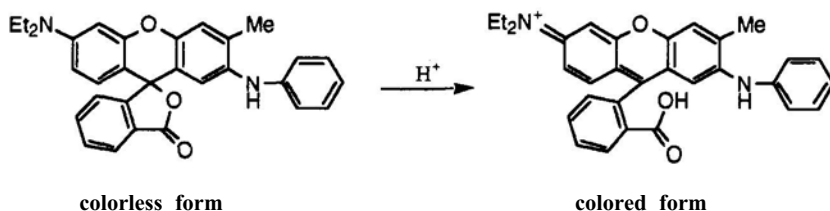


Figure 6.1. Color-formation reaction of fluoran 12.

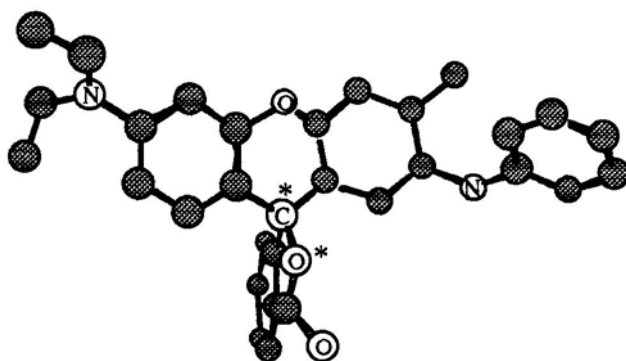


Figure 6.2. Perspective view of fluoran 12.

along the line of spiro-carbon (C^*) and oxygen atoms, and the phthalide moiety is almost perpendicular to the xanthene moiety. The $C^*—O^*$ length is 1.527 Å which is about 0.1 Å longer than the usual $C(sp^3)—O$ length. This elongation gives easy cleavage of the $C^*—O^*$ bond to open the lactone ring resulting in colored structure.

The color-formation reaction is not irreversible but reversible. Thus, the colored form can easily reproduce the colorless form by treating with base.

When solid organic compounds such as 4,4'-isopropylidenediphenol (Bisphenol A) are used as the acidic compound, higher alcohols can control the reversible color-formation reaction. For example, a molten mixture of fluoran 9 (1 part) and Bisphenol A (5 parts) develops vermilion color. In the presence of 1-hexadecanol (94 parts) the resulting mixture indefinitely repeats colorless and colored forms above and below ca.48°C or the melting point of 1-hexadecanol, respectively (Figure 6.3). That is, below the melting point of 1-hexadecanol the affinity of the fluoran compound with Bisphenol A is stronger than that of 1-hexadecanol with Bisphenol A resulting in the color-formation reaction. On the other hand, above the melting point of 1-hexadecanol it functions as an inhibitor of the color-

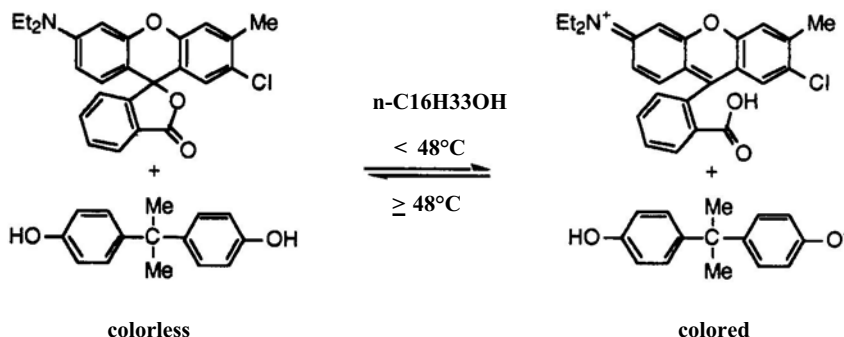


Figure 6.3. Reversible color-formation reaction between fluoran **9** and Bisphenol A.

formation reaction. Besides higher alcohols, certain esters, ethers, ketones, nitriles, and other compounds can also control the reversible color-formation reaction. This remarkable property is used as a thermoindicator.⁹

Figure 6.4 shows the absorption spectra of the colored form of fluoran **12** developed by tin(IV) chloride in methyl alcohol. It is clear that the

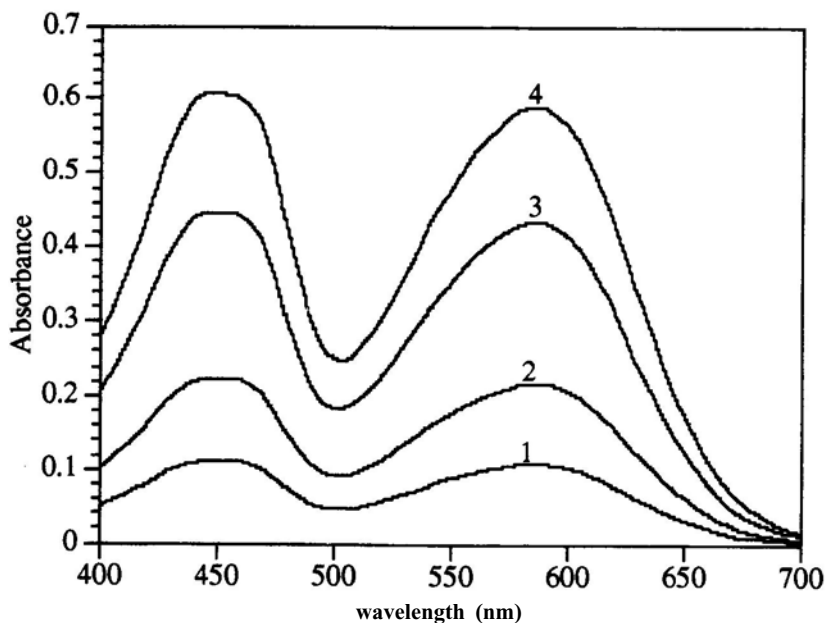


Figure 6.4. Absorption spectra of colored fluoran **12** (31.5 μmol/liter in methyl alcohol) developed by tin(IV) chloride (curve 1, 2.5 μmol; curve 2, 5 μmol; curve 3, 10 μmol; curve 4, 20 μmol).

colored form of **12** increases proportionally with increasing amount of tin(IV) chloride and the color formation is complete by ca. 0.5 mol of tin(IV) chloride per mol of **12** to give the absorptivities of ca. 40 liters $\text{g}^{-1} \text{cm}^{-1}$ at 450 and 585 nm.

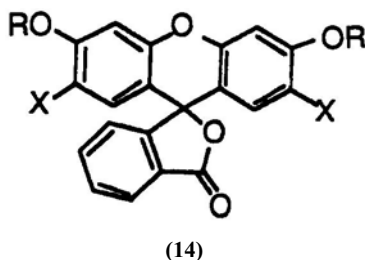
6.2.2. Effects of Substituents on Color

Fluoran compounds have the remarkable feature of giving a wide variety of colors depending on their substituent(s).

The following will discuss the effect of substituents for each developing color.

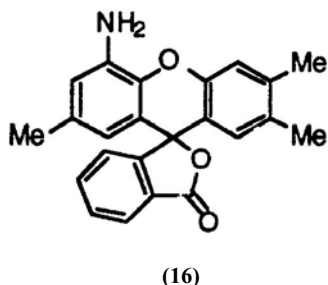
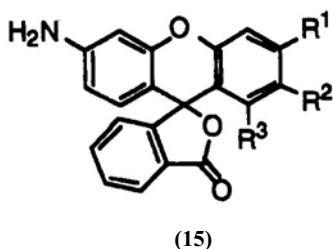
6.2.2.1. Yellow Developing Fluorans

Fluoran compounds having two alkoxy groups at 3'- and 6'-positions develop yellow color, but the color intensity is not very high. These include 3',6'-dimethoxyfluoran (**14**; $\text{R} = \text{CH}_3$, $\text{X} = \text{H}$),¹⁰ 2',7'-dichloro-3',6'-dimethoxyfluoran (**14**; $\text{R} = \text{CH}_3$, $\text{X} = \text{Cl}$),¹⁰ 3',6'-diethoxyfluoran (**14**; $\text{R} = \text{C}_2\text{H}_5$, $\text{X} = \text{H}$),¹⁰ 3',6'-dibenzoyloxyfluoran (**14**; $\text{R} = \text{C}_6\text{H}_5\text{CH}_2$, $\text{X} = \text{H}$),¹⁰ 3',6'-bis(2-chloroethoxy)fluoran (**14**; $\text{R} = \text{ClC}_2\text{H}_4$, $\text{X} = \text{H}$),¹¹ and 3',6'-bis-(2-cyanoethoxy)fluoran (**14**; $\text{R} = \text{NCC}_2\text{H}_4$, $\text{X} = \text{H}$).¹¹



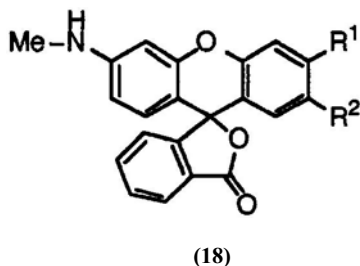
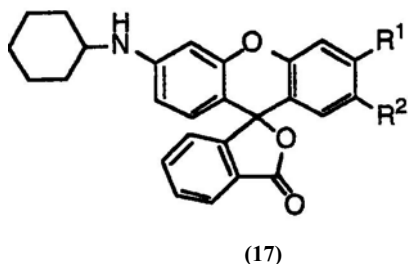
Fluoran compounds having an unsubstituted amino group at 3'-position also develop reddish yellow color. These include 6'-amino-2'-*t*-butylfluoran (**15**; $\text{R}^1, \text{R}^3 = \text{H}$, $\text{R}^2 = t\text{-C}_4\text{H}_9$),¹² 6'-amino-2'-*t*-butyl-3'-methylfluoran (**15**; $\text{R}^1 = \text{CH}_3$, $\text{R}^2 = t\text{-C}_4\text{H}_9$, $\text{R}^3 = \text{H}$),¹² 6'-amino-1',3'-dimethylfluoran (**15**; $\text{R}^1, \text{R}^3 = \text{CH}_3$, $\text{R}^2 = \text{H}$),¹² 6'-amino-2',3'-dimethylfluoran (**15**; $\text{R}^1, \text{R}^2 = \text{CH}_3$, $\text{R}^3 = \text{H}$),¹² and 3'-amino-6'-chlorofluoran (**15**; $\text{R}^1 = \text{Cl}$, $\text{R}^2, \text{R}^3 = \text{H}$)¹³.

On the other hand, if fluoran compounds have an unsubstituted amino group at 4-position such as 5'-amino-2',3',7'-trimethylfluoran (**16**),¹² they develop greenish blue color.



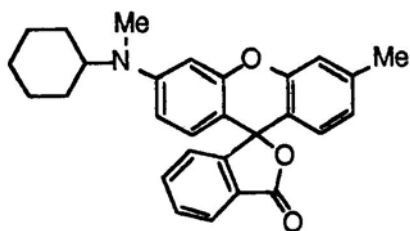
6.2.2.2. Orange Developing Fluorans

Fluoran compounds having a monosubstituted amino group at 3'-position generally develop orange color. Cyclohexyl group is most desirably used as the substituent on amino groups, though linear alkyl and aralkyl groups are also employed to give orange color. These include 2'-chloro-6'-cyclohexylaminofluoran (**17**; R¹ = H, R² = Cl),⁴ 3'-chloro-6'-cyclohexylaminofluoran (**17**; R¹ = Cl, R² = H),¹⁴ 6'-cyclohexylamino-2'-methylfluoran (**17**; R¹ = H, R² = CH₃),⁴ 2'-chloro-6'-methylaminofluoran (**18**; R¹ = H, R² = Cl),⁴ and 3'-chloro-6'-methylaminofluoran (**18**; R¹ = Cl, R² = H).¹³ Chlorine at 2'-position produces a smaller bathochromic shift than that at 3'-position.

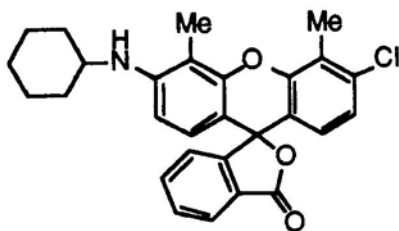


In addition, 3'-(*N*-cyclohexyl-*N*-methylamino)-6'-methylfluoran (**19**)⁴ develops orange color, whereas fluoran compounds having a disubstituted amino group at 3'-position generally develop red color as described in Section 6.2.2.3.

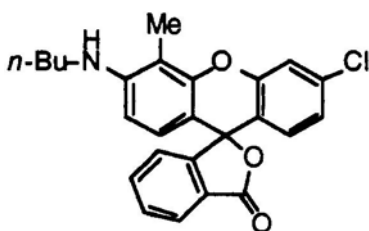
On the other hand, a methyl group adjacent to an amino group at 3'-position produces a bathochromic shift. Thus, 3'-chloro-6'-cyclohexylamino-4',5'-dimethylfluoran (**20**),¹⁴ 3'-*n*-butylamino-6'-chloro-4'-methylfluoran (**21**),¹⁵ etc. develop vermilion color.



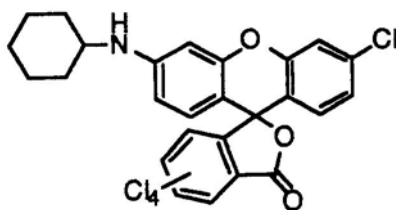
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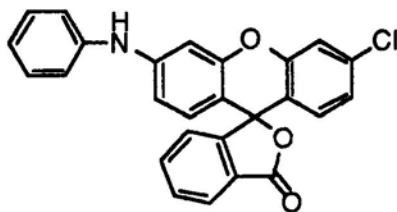
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(22)

In addition, chlorine on the phthalide moiety also gives a bathochromic shift. Thus, 3'-cyclohexylamino-4,5,6,6',7-pentachlorofluoran (**22**)¹⁴ develops red color.

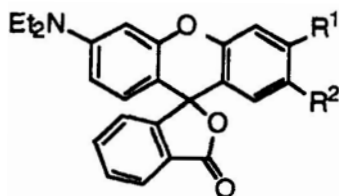
As a matter of course, replacement of (cyclo)alkylamino groups with arylamino groups will result in a bathochromic shift. For example, 3'-anilino-6'-chlorofluoran (**23**)¹³ develops yellowish red color.



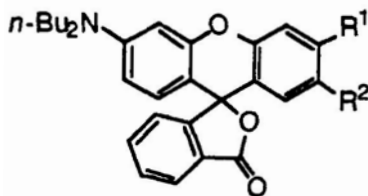
(23)

6.2.2.3. Red Developing Fluorans

Fluoran compounds having a dialkylamino group at 3'-position generally develop color from yellowish red to vermilion. These include



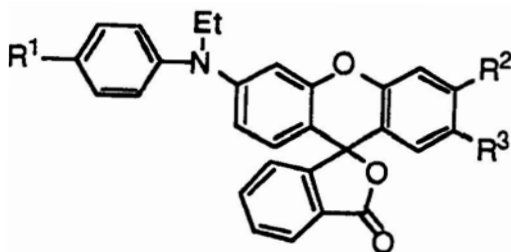
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(25)

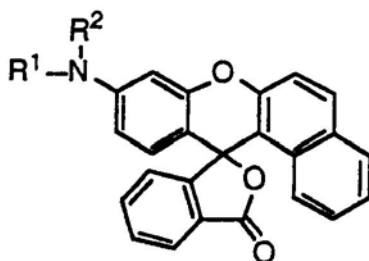
2'-chloro-6-diethylaminofluoran (**24**; $R^1 = \text{H}$, $R^2 = \text{Cl}$),¹⁶ 2'-chloro-6'-diethylamino-3'-methylfluoran (**24**; $R^1 = \text{CH}_3$, $R^2 = \text{Cl}$),¹⁷ 6'-diethylamino-2',3'-dimethylaminofluoran (**24**; $R^1, R^2 = \text{CH}_3$),¹² 6'-diethylamino-2'-methoxyfluoran (**24**; $R^1 = \text{H}$, $R^2 = \text{CH}_3\text{O}$),¹² 3'-diethylamino-6'-methoxyfluoran (**24**; $R^1 = \text{CH}_3\text{O}$, $R^2 = \text{H}$),¹⁸ 6'-diethylamino-2'-phenylfluoran (**24**; $R^1 = \text{H}$, $R^2 = \text{C}_6\text{H}_5$),¹⁹ 6'-diethylamino-2'-methylthiofluoran (**24**; $R^1 = \text{H}$, $R^2 = \text{CH}_3\text{S}$),²⁰ 2'-chloro-6'-di-*n*-butylamino-3'-methylfluoran (**25**; $R^1 = \text{CH}_3$, $R^2 = \text{Cl}$),²¹ and 3'-chloro-6'-di-*n*-butylamino-2'-methylfluoran (**25**; $R^1 = \text{Cl}$, $R^2 = \text{CH}_3$).²¹

Fluoran compounds having an *N*-alkyl-*N*-arylamino group at 3'-position such as 2'-chloro-6'-(*N*-ethyl-4-methylanilino)fluoran (**26**; $R^1 = \text{CH}_3$, $R^2 = \text{H}$, $R^3 = \text{Cl}$),²² 6'-(*N*-ethyl-4-methylanilino)-2'-methoxyfluoran (**26**; $R^1 = \text{CH}_3$, $R^2 = \text{H}$, $R^3 = \text{CH}_3\text{O}$),²² and 6'-(4-chloro-*N*-ethylanilino)-2',3'-dimethylfluoran (**26**; $R^1 = \text{Cl}$, $R^2, R^3 = \text{CH}_3$)²² also develop vermilion color, but these color tones are more bathochromic because of longer conjugated double bond system.



(26)

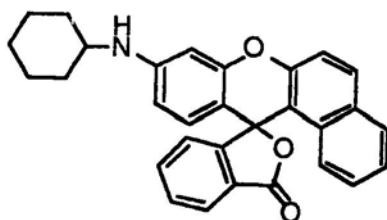
Benzofluoran compounds develop more bathochromic color than the corresponding fluoran compounds because of the longer conjugated system. Thus, 9'-diethylaminobenzo[*a*]fluoran (**27**; $R^1, R^2 = \text{C}_2\text{H}_5$),²⁰ 9'-(*N*-ethyl-



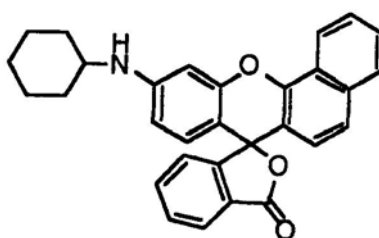
(27)

N-isopentylamino)benzo[*a*]fluoran (27; $R^1 = C_2H_5$, $R^2 = i-C_5H_{11}$),²³ etc. develop bluish red color.

In addition, 9'-cyclohexylaminobenzo[*a*]fluoran (28),²⁴ 10'-cyclohexylbenzo[*c*]fluoran (29),²⁴ etc. develop red color, despite the secondary amino group that contributes generally orange color.

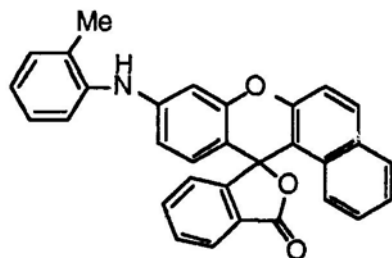


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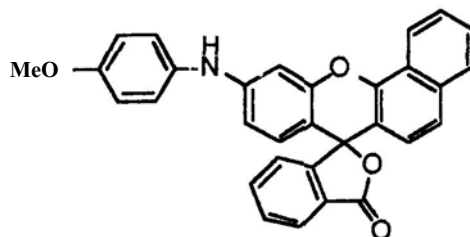


(29)

Benzofluoran compounds having an arylamino group develop much more bathochromic colors. Thus, 9'-(2-methylanilino)benzo[*a*]fluoran (30),²⁴ 10'-(4-methoxyanilino)benzo[*c*]fluoran (31),²⁴ etc. develop violet color.

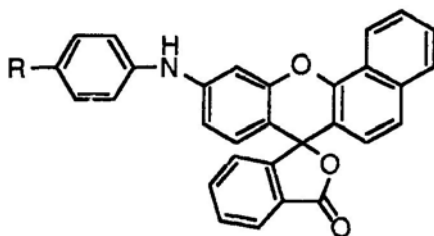


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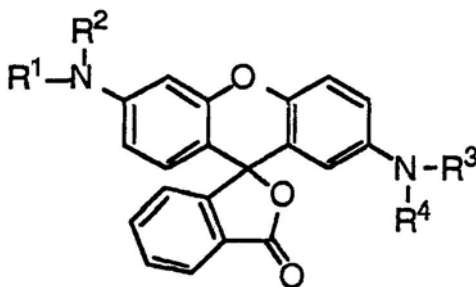
(31)

If the arylamino group is substituted with an appropriate group to extend the conjugated double bond system, blue color can also be obtained. For example, 10'-(4-anilinoanilino)benzo[*c*]fluoran (**32**; $R = C_6H_5NH$)²⁴ and 10'-(4-styrylanilino)benzo[*c*]fluoran (**32**; $R = C_6H_5CH=CH$)²⁵ develop blue color.



(32)

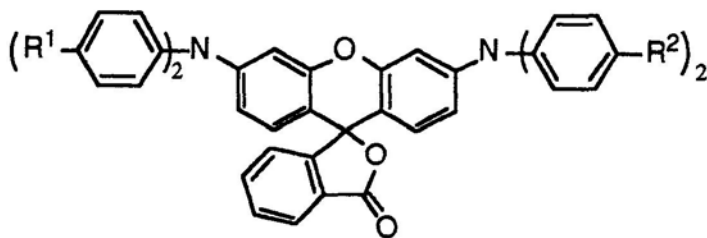
In addition, fluoran compounds having two amino groups at 2'- and 6'-positions develop red color when the 2'-amino group is an unsubstituted or acyl-substituted amino group. These include 2'-amino-6'-diethylaminofluoran (**33**; $R^1, R^2 = C_2H_5, R^3, R^4 = H$),⁵ 2'-acetamino-6'-diethylaminofluoran (**33**; $R^1, R^2 = C_2H_5, R^3 = H, R^4 = CH_3CO$),²⁶ 2'-(*N*-acetylanilino)-6'-diethylaminofluoran (**33**; $R^1, R^2 = C_2H_5, R^3 = C_6H_5, R^4 = CH_3CO$),²⁷ 2'-(*N*-benzoyl-*N*-methylanilino)-6'-diethylaminofluoran (**33**; $R^1, R^2 = C_2H_5, R^3 = CH_3, R^4 = C_6H_5CO$),²⁸ and 2'-acetamino-6'-(*N*-methylanilino)fluoran (**33**; $R^1 = CH_3, R^2 = C_6H_5, R^3 = H, R^4 = CH_3CO$).²²



(33)

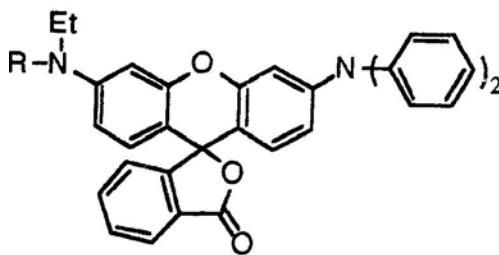
6.2.2.4. Blue Developing Fluorans

Fluoran compounds having two diarylamino groups at 3'- and 6'-positions generally develop blue tone colors. For example, 3',6'-bis-(diphenylamino)fluoran (**34**; $R^1, R^2 = H$)²⁹ develops reddish blue color, and 3'-diphenylamino-6'-di-*p*-tolylaminofluoran (**34**; $R^1 = H, R^2 = CH_3$)²⁹ and 3',6'-bis(di-*p*-tolylamino)fluoran (**34**; $R^1, R^2 = CH_3$)²⁹ blue color.



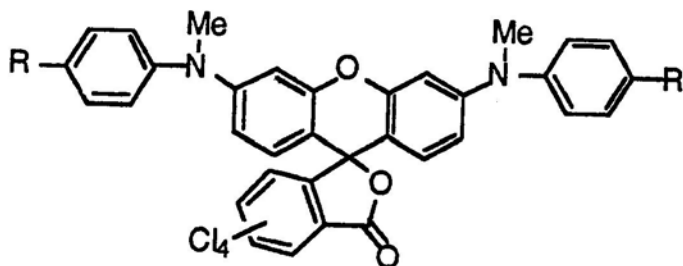
(34)

If at least one of the aryl groups at 3'-position is replaced with an alkyl group, then the developed color is more reddish as a result of a hypsochromic shift. Thus, 3'-diethylamino-6'-diphenylaminofluoran (**35**; $R = C_2H_5$)²⁹ and 3'-diphenylamino-6'-(*N*-ethyl-*p*-toluidino)fluoran (**35**; $R = 4-CH_3C_6H_4$)²⁹ develop reddish violet and bluish violet colors, respectively.



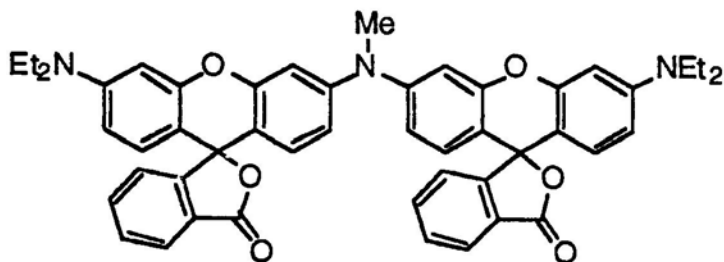
(35)

However, introducing halogens on the benzene ring of the phthalide moiety contributes a bathochromic shift. Thus, 3',6'-bis(*N*-methylanilino)-4,5,6,7-tetrachlorofluoran (**36**; $R = H$)³⁰ and 3',6'-bis(4-chloro-*N*-methylanilino)-4,5,6,7-tetrachlorofluoran (**36**; $R = Cl$)³⁰ still develop purplish blue and blue colors, respectively.



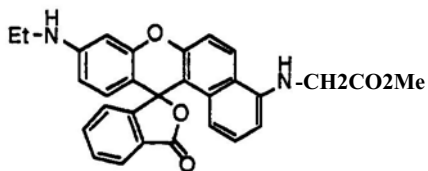
(36)

In addition, 3,3'-*N*-methyliminobis(6'-diethylaminofluoran) (37)³¹ develops reddish blue color, in spite of no halogen atoms on the phthalide moiety.

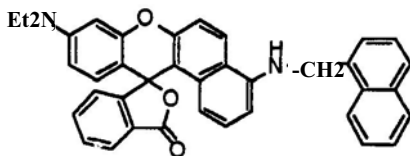


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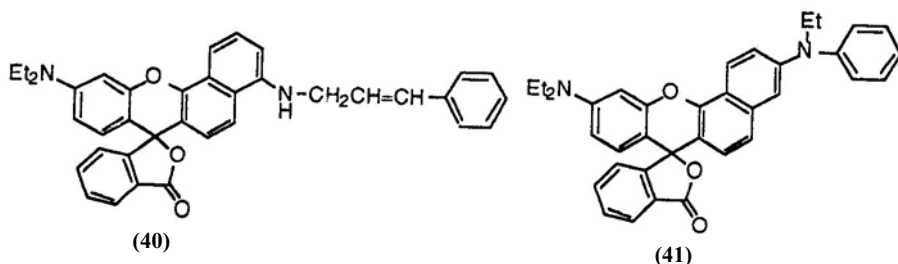
Some benzofluorans having two amino groups also develop blue color. These include 9'-ethylamino-4'-(methoxycarbonylmethylamino)benzo[*a*]fluoran (38),³² 9'-diethylamino-4'- α -naphthylmethylaminobenzo[*a*]fluoran (39),³² 4'-cinnamylamino-10'-diethylaminobenzo[*c*]fluoran (40),³² and 10'-diethylamino-3'-(*N*-ethylanilino)benzo[*c*]fluoran (41).³³



(38)

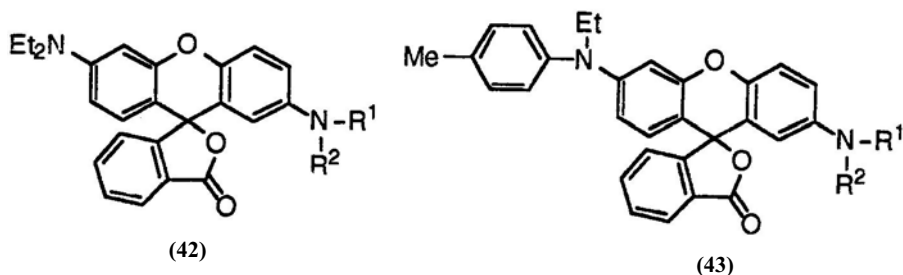


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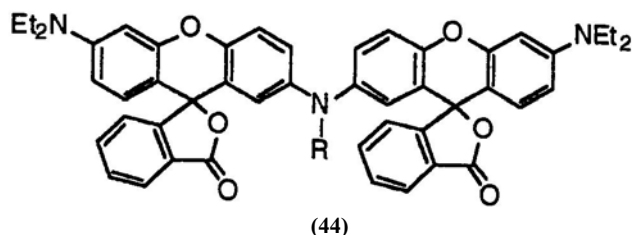


6.2.2.5. Green Developing Fluorans

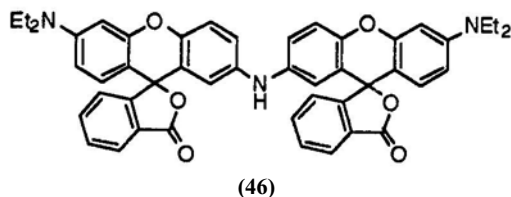
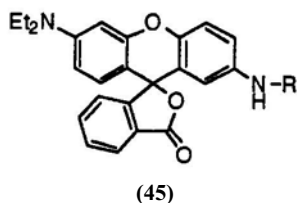
Fluoran compounds having two tertiary amino groups at 2'- and 6'-positions generally develop green color. For example, 2',6'-bis(diethylamino)fluoran (**42**; $R^1, R^2 = C_2H_5$),⁵ 2'-(*N*-benzyl-*N*-ethylamino)-6'-diethylaminofluoran (**42**; $R^1 = C_2H_5, R^2 = C_6H_5CH_2$),⁵ 2'-dibenzylamino-6'-diethylaminofluoran (**42**; $R^1, R^2 = C_6H_5CH_2$),⁵ 6'-diethylamino-2'-diphenethylaminofluoran (**42**; $R^1, R^2 = C_6H_5C_2H_4$),³⁴ 6'-diethylamino-2'-(*N*-methylanilino)fluoran (**42**; $R^1 = CH_3, R^2 = C_6H_5$),³⁶ 2'-dibenzylamino-6'-(*N*-ethyl-4-methylanilino)fluoran (**43**; $R^1, R^2 = C_6H_5CH_2$),²² 6'-(*N*-ethyl-4-methylanilino)-2'-(*N*-methylanilino)fluoran (**43**; $R^1 = CH_3, R^2 = C_6H_5$),²² 2'-diallylamino-6'-(*N*-ethyl-4-methylanilino)fluoran (**43**; $R^1, R^2 = CH_2=CHCH_2$),³⁷ 2'-di-*n*-propylamino-6'-(*N*-ethyl-4-methylanilino)fluoran (**43**; $R^1, R^2 = n-C_3H_7$),³⁷ 2'-dicinnamylamino-6'-(*N*-ethyl-4-methylanilino)fluoran (**43**; $R^1, R^2 = C_6H_5CH=CHCH_2$),³⁷ etc. develop green color.



In addition, 2',2''-*N*-ethyliminobis(6'-diethylaminofluoran) (**44**; $R = C_2H_5$),³⁸ 2',2''-*N*-benzyliminobis(6'-diethylaminofluoran) (**44**; $R = C_6H_5CH_2$),³⁸ 2',2''-*N*-cinnamyliminobis(6'-diethylaminofluoran) (**44**; $R = C_6H_5CH=CHCH_2$),³⁸ 2',2''-*N*-propargyliminobis(6'-diethylaminofluoran) (**44**; $R = CH=CCH_2$),³⁸ etc. develop green color.

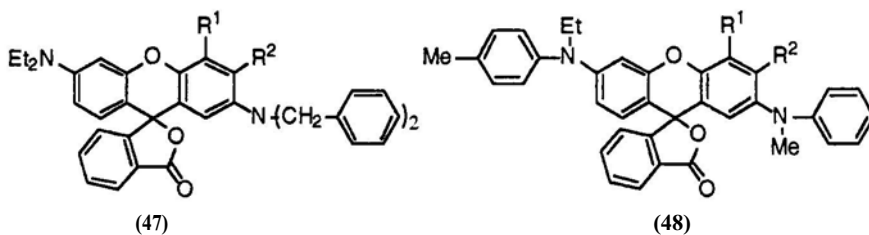


When secondary amino groups are employed in the place of tertiary amino groups at 2'-position, the fluoran compounds develop dark green or greenish black color. These include 2'-*n*-butylamino-6'-diethylaminofluoran (**45**; $R = n\text{-C}_4\text{H}_9$),⁵ 6'-diethylamino-2'-*n*-octylaminofluoran (**45**; $R = n\text{-C}_8\text{H}_{17}$),³⁹ 2'-allylamino-6'-diethylaminofluoran (**45**; $R = \text{CH}_2=\text{CHCH}_2$),³⁵ 2'-benzylamino-6'-diethylaminofluoran (**45**; $R = \text{C}_6\text{H}_5\text{CH}_2$),⁵ 6-diethylamino-2'-phenethylaminofluoran (**45**; $R = \text{C}_6\text{H}_5\text{C}_2\text{H}_4$),²⁰ 2'-cinnamylamino-6-diethylaminofluoran (**45**; $R = \text{C}_6\text{H}_5\text{CH}=\text{CHCH}_2$),³⁵ 2'-anilino-6'-diethylaminofluoran (**45**; $R = \text{C}_6\text{H}_5$),³⁹ and 2',2''-iminobis(6'-diethylaminofluoran) (**46**).³⁸

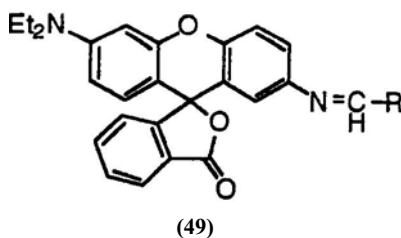


Introduction of an additional substituent such as alkyl, alkoxy, halogen, etc. at 3'-position has a large effect on color. That is, green color changes to red color when there is a tertiary amino group at 2'-position. Thus, 2'-dibenzylamino-6'-diethylamino-3'-methylfluoran (**47**; $R^1 = \text{H}$, $R^2 = \text{CH}_3$),⁴⁰ 2'-dibenzylamino-6'-diethylamino-3'-ethylfluoran (**47**; $R^1 = \text{H}$, $R^2 = \text{C}_2\text{H}_5$),³⁴ 3'-chloro-2'-dibenzylamino-6'-diethylaminofluoran (**47**; $R^1 = \text{H}$, $R^2 = \text{Cl}$),³⁴ 6'-(*N*-ethyl-4-methylanilino)-3'-methyl-2'-(*N*-methylanilino)fluoran (**48**; $R^1 = \text{H}$, $R^2 = \text{CH}_3$),²² etc. develop red color. If there is a secondary amino group at 2'-position, black color can be obtained: this will be discussed in Section 6.2.2.6. On the other hand, introduction of an additional substituent at 4'-position exerts little influence on color. Thus, 2'-dibenzylamino-6'-diethylamino-4'-methylfluoran (**47**; $R^1 = \text{CH}_3$, $R^2 = \text{H}$),³⁸ 4'-chloro-2'-dibenzylamino-6'-diethylaminofluoran (**47**; $R^1 = \text{Cl}$,

$R^2 = H$),³⁸ 2'-dibenzylamino-6'-diethylamino-4'-methoxyfluoran (47; $R^1 = CH_3O$, $R^2 = H$),⁴¹ 4'-chloro-6'-(*N*-ethyl-4-methylanilino)-2'-(*N*-methylanilino)fluoran (48; $R^1 = Cl$, $R^2 = H$),²² 6'-(*N*-ethyl-4-methylanilino)-4'-methyl-2'-(*N*-methylanilino)fluoran (48; $R^1 = CH_3$, $R^2 = H$),²² etc. still develop green color.



Replacement of amino groups at 2'-position with azomethine groups gives brown color. These include 6'-diethylamino-2'-ethylidenamino-fluoran (49; $R = CH_3$),⁴² 2'-(2-butenyldienamino)-6'-diethylaminofluoran (49; $R = CH_3CH=CH$),⁴² 2'-benzyldienamino-6'-diethylaminofluoran (49; $R = C_6H_5$),⁴² and 2'-cinnamyldienamino-6'-diethylaminofluoran (49; $R = C_6H_5CH=CH$).⁴²



6.2.2.6. Black Developing Fluorans

The most remarkable feature of fluoran compounds is producing singly black color, which can hardly be attained by any other class of leuco dyes.

One of the typical black developing fluoran compounds is 2'-anilino-6'-diethylamino-3'-methylfluoran (50)⁶ in which the methyl group at 3'-position plays a very important role. The parent structure of 50 is 2'-anilino-6'-

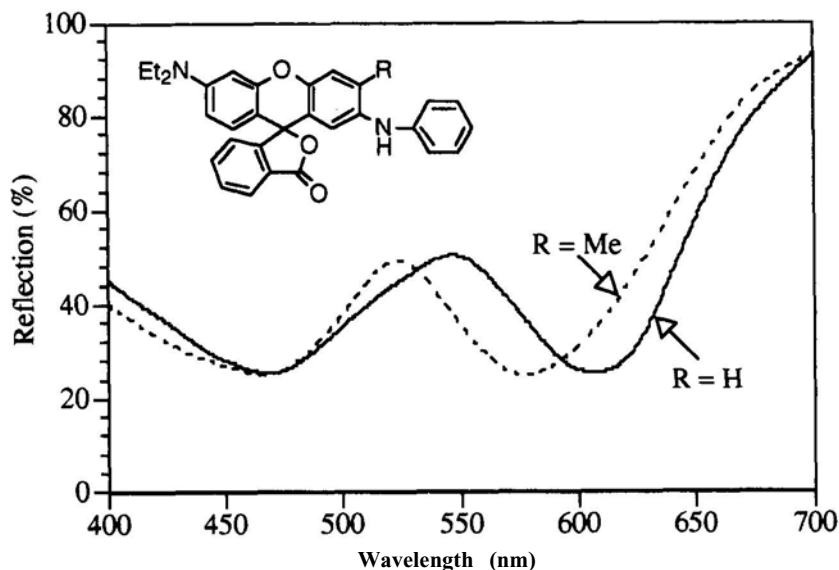
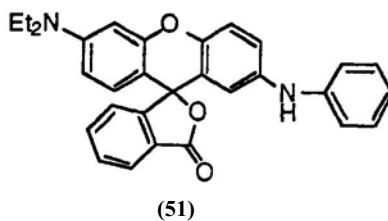
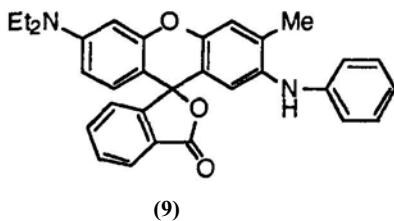


Figure 6.5. Reflection spectra of colored form of fluoran **50** and **51**.

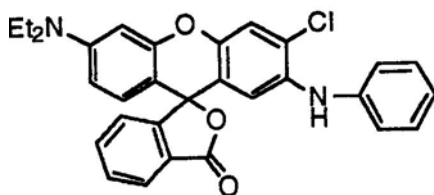
diethylaminofluoran (**51**), which colored form has two distinctive absorption maxima at 470 nm (yellow in color) and 610 nm (blue in color) in the visible region resulting in green color by the additivity of the two colors yellow and blue (Figure 6.5).



In fluoran **50**, the methyl group at 3'-position causes steric hindrance to the adjacent anilino group resulting in torsion of the anilino group from the xanthene plane. Consequently, electron transfer from the anilino group to the xanthene moiety is hindered more or less, resulting in hypsochromic shift of the absorption at 610 nm to 570 nm (violet in color). On the other

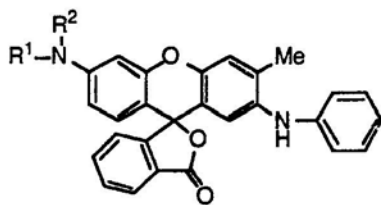
hand, the absorption at 470 nm is scarcely affected by the introduction of the methyl group. The two colors yellow and violet are complementary, and fortunately the two absorption maxima are nearly the same in absorbancy. Thus, **50** develops black color by the additivity of the complementary colors of yellow and violet (Figure 6.5).

Besides the methyl group, a chlorine atom at 3'-position gives the same effect. Thus, 2'-anilino-3'-chloro-6'-diethylaminofluoran (**52**)⁴³ also develops black color for the same reason.

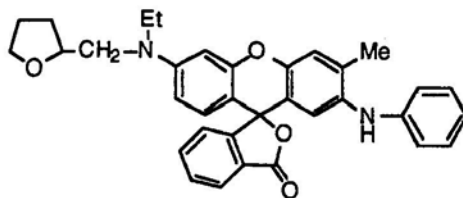


(52)

Today, many black developing fluoran compounds having a wide variety of substituents on the amino group at 6'-position are available. These include 2'-anilino-3'-methyl-6'-(*N*-methyl-*N*-*n*-propylamino)fluoran (**53**; $R^1 = \text{CH}_3$, $R^2 = n\text{-C}_3\text{H}_7$),⁴⁴ 2'-anilino-6'-(*N*-cyclohexyl-*N*-methylamino)-3'-methylfluoran (**53**; $R^1 = \text{CH}_3$, $R^2 = c\text{-C}_6\text{H}_{11}$),⁴⁵ 2'-anilino-6'-(*N*-ethyl-*N*-isobutylamino)-3'-methylfluoran (**53**; $R^1 = \text{C}_2\text{H}_5$, $R^2 = i\text{-C}_4\text{H}_9$),⁴⁶ 2'-anilino-6'-(*N*-ethyl-*N*-isopentylamino)-3'-methylfluoran (**53**; $R^1 = \text{C}_2\text{H}_5$, $R^2 = i\text{-C}_5\text{H}_{11}$),⁴⁷ 2'-anilino-6'-[*N*-(3-ethoxypropyl)-*N*-ethylamino]-3'-methylfluoran (**53**; $R^1 = \text{C}_2\text{H}_5$, $R^2 = \text{C}_2\text{H}_5\text{OC}_3\text{H}_6$),⁴⁸ 2'-anilino-6'-(*N*-ethyl-4-methylanilino)-3'-methylfluoran (**53**; $R^1 = \text{C}_2\text{H}_5$, $R^2 = 4\text{-CH}_3\text{C}_6\text{H}_4$),²² 2'-anilino-6'-(*N*-ethyl-*N*-tetrahydrofurfurylamino)-3'-methylfluoran (**54**),⁴⁹ 2'-anilino-6'-di-*n*-propylamino-3'-methylfluoran (**53**; $R^1, R^2 = n\text{-C}_3\text{H}_7$),⁵⁰



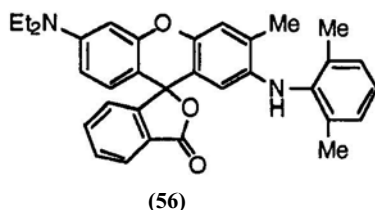
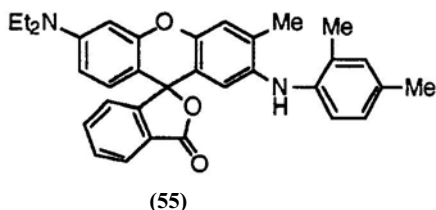
(53)



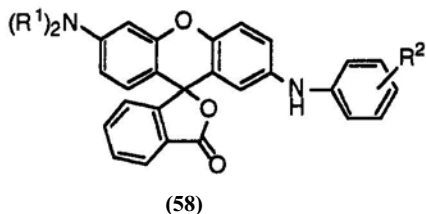
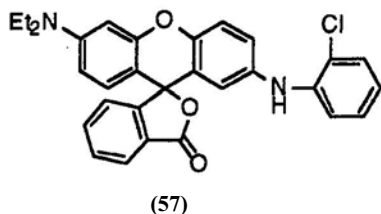
(54)

2'-anilino-6'-di-*n*-butylamino-3'-methylfluoran (**53**; $R^1, R^2 = n\text{-C}_4\text{H}_9$),^{51,52} 2'-anilino-6'-di-*n*-pentylamino-3'-methylfluoran (**53**; $R^1, R^2 = n\text{-C}_5\text{H}_{11}$),⁴⁷ 2'-anilino-3'-methyl-6'-pyrrolidinofluoran [**53**; $R^1, R^2 = (\text{CH}_2)_4$],⁵³ and 2'-anilino-3'-methyl-6'-piperidinofluoran [**53**; $R^1, R^2 = (\text{CH}_2)_5$].⁵³ Each has its own characteristics regarding solubility to organic solvents, affinity with acidic compounds, etc., though all are substantially similar in color tone.

Introduction of a methyl group on the anilino group at 2'-position has more than a little influence on color tone. For example, 6'-diethylamino-2'-(2,4-dimethylanilino)-3'-methylfluoran (**55**)⁵⁴ and 6'-diethylamino-2'-(2,6-dimethylanilino)-3'-methylfluoran (**56**)⁵⁵ develop greenish black and reddish black colors, respectively.

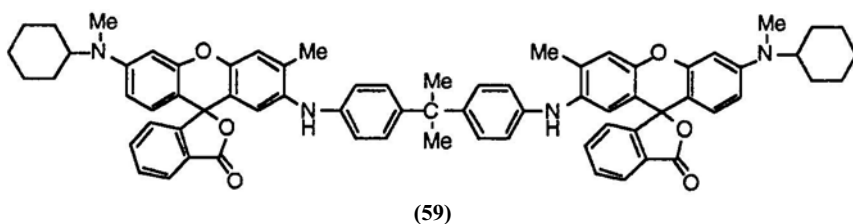


As was described above, the hindrance of electron transfer from the anilino group to the xanthene moiety causes black color development. Therefore, besides the steric hindrance between the adjacent methyl and anilino groups, introduction of an electron-attracting group on the anilino group also causes the hindrance of electron transfer resulting in black color development. For example, 2'-(2-chloroanilino)-6'-diethylaminofluoran (**57**)⁵⁶ is another typical example of black developing fluoran compounds. Additional black developing fluoran compounds having an electron-attracting group on the anilino group are 2'-(2-chloroanilino)-6'-di-*n*-butylaminofluoran (**58**; $R^1 = n\text{-C}_4\text{H}_9$, $R^2 = 2\text{-Cl}$),⁵⁷ 6'-diethylamino-2'-(2-fluoroanilino)fluoran (**58**; $R^1 = \text{C}_2\text{H}_5$, $R^2 = 2\text{-F}$),⁵⁸

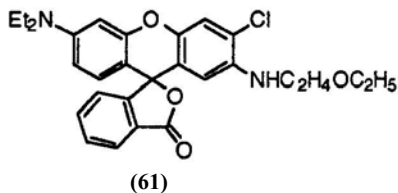
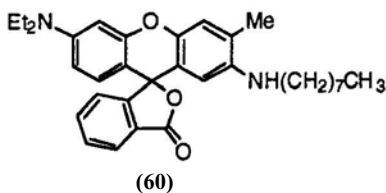


6'-di-*n*-butylamino-2'-(2-fluoroanilino)fluoran (**58**; $R_1 = n\text{-C}_4\text{H}_9$, $R^2 = 2\text{-F}$),⁵⁸ 6'-diethylamino-2'-(3-trifluoromethylanilino)fluoran (**58**; $R_1 = \text{C}_2\text{H}_5$, $R^2 = 3\text{-CF}_3$),⁵⁹ and 6'-diethylamino-2'-(2-methoxycarbonylanilino)fluoran (**58**; $R_1 = \text{C}_2\text{H}_5$, $R^2 = 2\text{-CH}_3\text{OCO}$).²⁰

In addition, dimer-type black developing fluoran compounds such as 2,2-bis(4-[6'-(*N*-cyclohexyl-*N*-methylamino)-3'-methylfluoran-2'-yl-amino]phenyl)propane (**59**)⁶⁰ are also proposed. Fluoran **59** has much lower solubility in organic solvents to improve image stability to plasticizer for use in thermosensitive recording label paper.

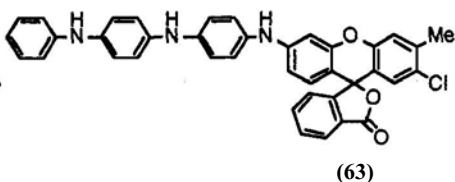
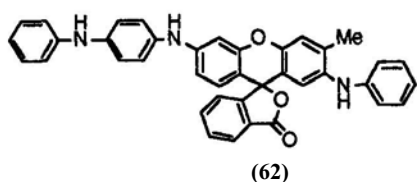


Alkylamino groups are also employed in place of anilino groups at 2'-position to give black color, though the color tone is a little greenish. These include 6'-diethylamino-3'-methyl-2'-*n*-octylaminofluoran (**60**),⁶¹ and 3'-chloro-6'-diethylamino-2'-(2-ethoxyethylamino)fluoran (**61**).⁶²

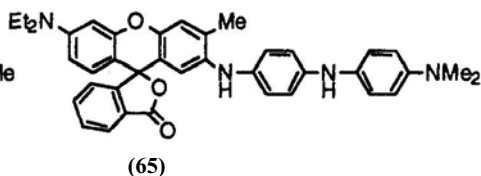
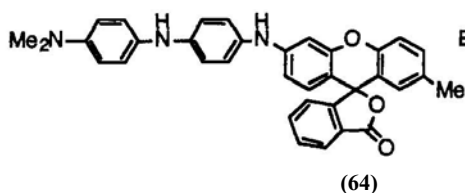


6.2.2.7. Near-Infrared-Absorbing Fluorans

Extension of conjugated double bond system at 2'- and/or 6'-positions makes it possible for fluoran compounds to have an absorption in the near infrared region up to 1200 nm. These include 2'-anilino-6-(4-anilinoanilino)-3'-methylfluoran (**62**),⁶³ 6'-[4-(4-anilinoanilino)anilino]-2'-chloro-3'-methylfluoran (**63**),⁷ 6'-[4-(4-dimethylaminoanilino)anilino]-2'-methylflu-



oran (64),⁶⁴ and 6'-diethylamino-2'-[4-(4-dimethylaminoanilino)anilino]-3'-methylfluoran (65).⁶⁵



6.2.3. Crystal Modification

Fluoran compounds have an optically active spiro-carbon atom. Consequently, some fluoran compounds, especially those having an alkylamino group of four or more carbon atoms at 3'-position, have been found to exhibit crystal modifications as determined by X-ray diffraction. Each crystal modification reveals different physical properties such as melting point, solubility, and affinity with acidic compounds, resulting in different characteristics regarding use for carbonless copying papers, thermosensitive recording papers, and the like.

Table 1 shows a few examples of fluoran compounds having crystal modifications.

6.3. SYNTHESIS OF FLUORAN COMPOUNDS

6.3.1. Reaction of Keto Acids with Phenols

The reaction of keto acids with phenols is mainly used to prepare fluoran compounds developing colors from orange to red.

That is, keto acids (66) react with a wide variety of phenols (67) to give 3'-aminofluorans (68) (Eq. 1).

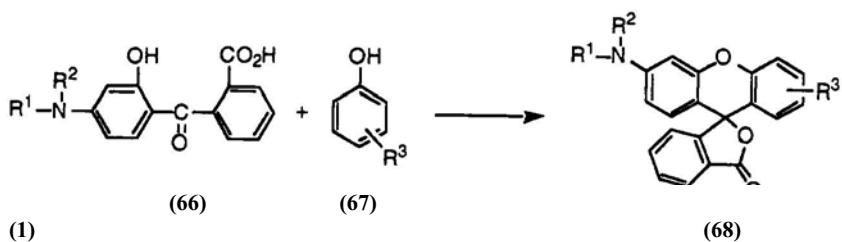
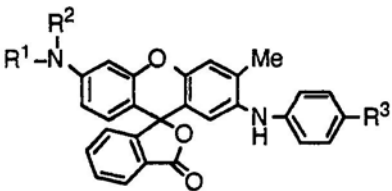
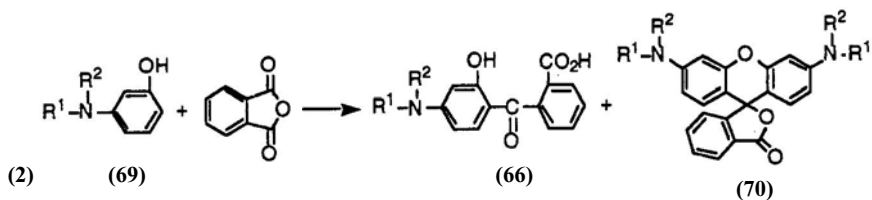


Table 1. Crystal Modifications of Fluoran Compounds



R ¹	R ²	R ³	mp °C		Ref.
			α-form	β-form	
CH ₃	<i>n</i> -C ₃ H ₇	H	175–177	178–181	66
C ₂ H ₅	<i>n</i> -C ₄ H ₉	H	162–164	181–183	67
<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	H	148–152	180–184	52
<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	F	135–137	169–171	68
<i>n</i> -C ₅ H ₁₁	<i>c</i> -C ₆ H ₁₁	H	136–141	168–171	67

The keto acids (66) having a tertiary amino group at 4-position are successfully prepared by the reaction of 3-*tert*-aminophenols (69) with phthalic anhydride in organic solvent such as benzene, toluene, or chlorobenzene at elevated temperature, though each keto acid has its own



characteristic reaction temperature, because some 3-*tert*-aminophenols can produce 3',6'-diaminofluorans (70) as a by-product at higher reaction temperature (Eq. 2).

Table 2 shows melting points of representative examples of the keto acids (66) having a tertiary amino group at 4-position. 2-(4-Diethylamino-2-hydroxybenzoyl)benzoic acid (66b) is the most popular among the keto acids.

On the other hand, the reaction of 3-*sec*-aminophenols (71) with phthalic anhydride does not give the corresponding keto acids (72). The keto acids (72) having a secondary amino group at 4-position are prepared by the reaction of 3-*sec*-aminophenols (71) with phthalimide at 150–220°C in the presence of boric acid, followed by hydrolysis of the intermediate carboxamide with aqueous sodium hydroxide (Eq. 3).

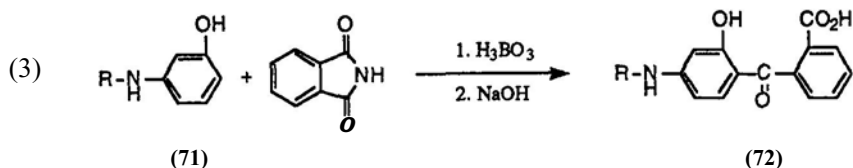


Table 3 shows melting points of a few representative keto acids (72).

The reaction of keto acids (66) with phenols (67) is usually carried out in 70–90% sulfuric acid at 50–150°C, or in an aromatic solvent such as benzene, toluene, or chlorobenzene at reflux in the presence

Table 2. Melting Points of Keto Acids (66)

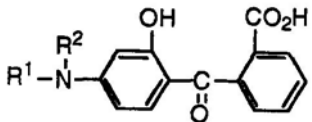
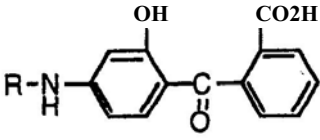
			
66	R ¹	R ²	mp °C
a	CH ₃	CH ₃	185–186
b	C ₂ H ₅	C ₂ H ₅	207–208
c	C ₂ H ₅	i-C ₄ H ₉	141–142
d	C ₂ H ₅	i-C ₅ H ₁₁	130–131
e	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	190–192
f	CH ₃	C ₆ H ₅	164–165
g	CH ₃	4-CH ₃ C ₆ H ₄	201–202
h	C ₂ H ₅	C ₆ H ₅	186–187
i	C ₂ H ₅	4-CH ₃ C ₆ H ₄	172–175

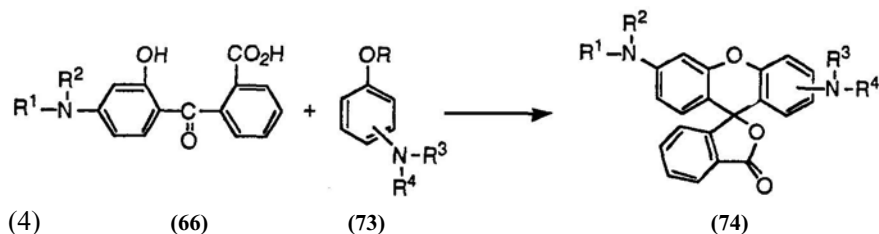
Table 3. Melting Points of Keto Acids (72)

		
72	R	mp°C
a	<i>c</i> -C ₆ H ₁₁	140–142
b	C ₆ H ₅ CH ₂	190–192
c	C ₆ H ₅	184–186
d	4-CH ₃ C ₆ H ₄	204–205
e	4-C ₂ H ₅ C ₆ H ₄	174–176
f	4- <i>n</i> -C ₄ H ₉ C ₆ H ₄	170–171

of a small amount of concentrated sulfuric acid. Many phenols such as *p*-cresol, 3,5-dimethylphenol, 2,3,5-trimethylphenol, *p*-chlorophenol, *p*-chloro-*m*-cresol, β -naphthol, or 6-bromo- β -naphthol give the corresponding 3'-aminofluorans (**68**) in good yield, though phenol and α -naphthol give lower yield. In the case of 1-bromo- β -naphthol, the bromine atom is liable to eliminate in acidic media resulting in the formation of the same fluoran compound derived from β -naphthol.

Table 4 shows results of a few representative 3'-diethylaminofluorans (**68**; R¹, R² = C₂H₅) prepared by the reaction of 2-(4-diethylamino-2-hydroxybenzoyl)benzoic acid (**66b**) with phenols.

The keto acids (**66**) also react with aminophenols (**73**; R = H) or aminoanisoles (**73**; R = CH₃) to give diaminofluorans (**74**) (Eq. 4).



In this case, it is preferable to carry out the reaction in concentrated sulfuric acid at up to 60 °C to achieve good results.

Table 4. 3'-Diethylaminofluorans (**68**)

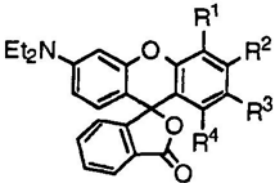
						
68	R ¹	R ²	R ³	R ⁴	Yield (%)	mp°C
a	H	H	CH ₃	H	82	160–161
b	CH ₃	CH ₃	H	CH ₃	85	236–237
c	Cl	H	CH ₃	H	84	207–209
d	H	CH ₃	Cl	H	85	235–236
e	H	H	Cl	H	84	174–176
f	H	H	—CH=CH—CH=CH—		90	220–221
g	H	H	—CH=CBr—CH=CH—		85	240–241
h	—CH=CH—CH=CH—		H	H	34	191–192

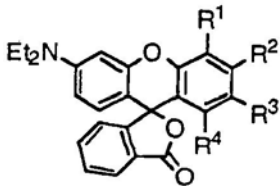
Table 5 shows results of a few representative of diaminofluorans (**74**) prepared by the reaction of the keto acid (**66b**) with aminophenols or aminoanisoles. 2'-Amino-6'-diethylaminofluoran (**74a**) is an important precursor for 2'-dibenzylamino-6'-diethylaminofluoran developing green color.

Preparation of 2-(4-Diethylamino-2-hydroxybenzoyl) benzoic acid (66B). A mixture of 3-diethylaminophenol (1 mol) and phthalic anhydride (1.1 mol) in toluene (400 ml) was stirred at reflux for 5 h. After being cooled, the precipitate was filtered off, washed with methanol, and dried to give 2-(4-diethylamino-2-hydroxybenzoyl)benzoic acid in 90% yield as a pale pink powder, mp 207–208 °C.

Preparation of 2-(4-Di-n-butylamino-2-hydroxybenzoyl) benzoic acid (66e). A mixture of 3-di-n-butylaminophenol (1 mol) and phthalic anhydride (1.2 mol) in toluene (250 ml) was stirred at 65–70°C for 24 h. After being cooled, the precipitate was filtered off, washed with toluene followed by methanol, and dried to give 2-(4-di-n-butylamino-2-hydroxybenzoyl)-benzoic acid in 85% yield as a pale pink powder, mp 190–192°C.

Preparation of 2-[2-Hydroxy-4-(4-methylanilino)benzoyl]benzoic acid (72d). To a molten mixture of 3-(4-methylanilino)phenol (1 mol) and

Table 5. Diaminofluorans (74)

						
74	R ¹	R ²	R ³	R ⁴	Yield(%)	mp°C
a	H	H	NH ₂	H	90	213–215
b	CH ₃	H	NH ₂	H	73	175–178
c	H	C1	C ₂ H ₅ OC ₂ H ₄ NH	H	70	188–190
d	H	H	<i>n</i> -C ₈ H ₁₇ NH	H	75	127–128
e	H	H	C ₆ HCH ₂ NH	H	65	168–169
f	H	H	—CH=C(NH ₂)—CH=CH—		86	243–244
g	—CH=CH—CH=CH—		NH ₂	H	46	227–229

phthalimide (1 mol) heated at 150°C was added boric acid (2 mol). The resulting mixture was stirred at 200–210 °C, while water formed was distilled out. The mixture solidified within 1 h. The solidified mixture was then heated with 10% aqueous sodium hydroxide (3500ml) for 4h to hydrolyze the carboxamide; a clear solution was formed followed by deposition of a new precipitate or sodium salt of the keto acid. The precipitate was filtered off, washed with water, dispersed in water (3000 ml), and made pH 4 by hydrochloric acid. After being refluxed for 15min, the solid part was filtered off, washed with hot water, dried, and then recrystallized from toluene/methanol (1:1) to give 2-[2-hydroxy-4-(4-methylanilino)-benzoyl]benzoic acid in 50% yield as a pale brown-green powder, mp 204–205 °C.

Preparation of 6'-Diethylamino-1',3',4'-trimethylfluoran (68b). A mixture of 2-(4-diethylamino-2-hydroxybenzoyl)benzoic acid (0.1 mol), 2,3,5-trimethylphenol (0.1 mol), and 90% sulfuric acid (150 g) was stirred at 50–55°C for 5 h, and poured into water (1500ml). The precipitate was filtered off, washed with water, and then refluxed with a mixture of toluene (400ml) and 5% aqueous sodium hydroxide (200ml) for 30min. The toluene layer was separated, washed with hot water, concentrated, and the residue refluxed with methanol (200 ml) for 30 min. After being cooled, the precipitate was filtered off, washed with methanol, and dried to give 6'-

diethylamino-1',3',4'-trimethylfluoran in 85% yield as an off-white powder, mp 236–237 °C.

Preparation of 2'-Chloro-6'-diethylamino-3'-methylfluoran (68d). A mixture of 2-(4-diethylamino-2-hydroxybenzoyl)benzoic acid (0.1 mol), *p*-chloro-*m*-cresol (0.1 mol), and 85% sulfuric acid (150 g) was stirred at 110–120°C for 5 h, and poured into water (1500ml). The precipitate was filtered off, washed with water, and then refluxed with a mixture of toluene (500ml) and 5% aqueous sodium hydroxide (200ml) for 1 h. The toluene layer was then worked up in the same manner as above to give 2'-chloro-6'-diethylamino-3'-methylfluoran in 85% yield as a white powder, mp 235–236°C.

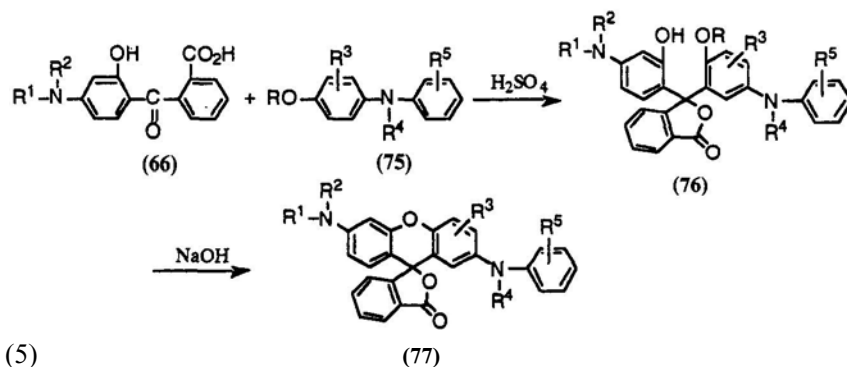
Preparation of 9'-Diethylaminobenzo[a]fluoran (68f). A mixture of 2-(4-diethylamino-2-hydroxybenzoyl)benzoic acid (0.1 mol) and β -naphthol (0.1 mol) in toluene (200 ml) containing concentrated sulfuric acid (5 ml) was stirred at reflux for 3 h, while water formed was removed as an azeotropic mixture with toluene. The mixture was diluted with toluene (200ml), made alkaline by 10% aqueous sodium hydroxide, and refluxing continued for another 1 h. The toluene layer was then worked up in the same manner as above to give 9'-diethylaminobenzo[a]fluoran in 90% yield as a white powder, mp 200–201 °C.

Preparation of 2'-Amino-6'-diethylaminofluoran (74a). A mixture of 2-(4-diethylamino-2-hydroxybenzoyl)benzoic acid (0.1 mol), *p*-anisidine (0.1 mol), and concentrated sulfuric acid (100 g) was stirred at 50 °C for 24 h. After being cooled, the mixture was poured into water (500 ml), and made alkaline by 20% aqueous sodium hydroxide. The precipitate was filtered off, washed with water, dried, and then recrystallized from toluene to give 2'-amino-6'-diethylaminofluoran in 90% yield as an off-white powder, mp 213–215 °C.

*Preparation of 6'-Diethylamino-2'-*n*-octylaminofluoran (74d).* To a solution of 2-(4-diethylamino-2-hydroxybenzoyl)benzoic acid (0.1 mol) in 98% sulfuric acid (150 g) was added *p*-*n*-octylaminoanisole (0.1 mol) in limited amounts, while the temperature was maintained not to rise above 30 °C. The resulting mixture was stirred at room temperature for 20 h, and poured into ice water (1000 ml). The resinous precipitate was collected by decantation, and then refluxed with a mixture of toluene (250ml) and 20% aqueous sodium hydroxide (100 g) for 1 h. The toluene layer was separated, washed with hot water, concentrated, and the residue recrystallized from isopropanol (100 ml) to give 6'-diethylamino-2'-*n*-octylaminofluoran in 75% yield as a white powder, mp 127–128 °C.

6.3.2. Reaction of Keto Acids with 4-Alkoxydiphenylamines

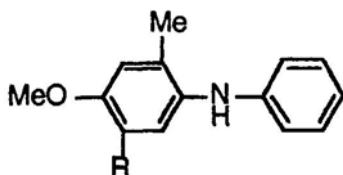
The reaction of the keto acids (**66**) with 4-alkoxydiphenylamines (**75**; R = CH₃, C₂H₅) is widely used to prepare fluoran compounds developing green or black colors. The reaction in concentrated sulfuric acid gives intermediate phthalide compounds (**76**), which are then treated with base to convert into 2'-anilino-6'-aminofluorans (**77**) (Eq. 5).



It is essential that the temperature of the first step not exceed 35 °C to minimize undesirable decomposition of the 4-alkoxydiphenylamines. In addition, the 4-alkoxydiphenylamines should be added to a solution of the keto acids in sulfuric acid. The reverse order of addition does not produce good results, because the 4-alkoxydiphenylamines are liable to decompose in sulfuric acid even at lower temperature. On the other hand, the phthalides are stable to a considerable extent in sulfuric acid at 35°C or below. The reaction is substantially completed in a few hours after dissolution of the 4-alkoxydiphenylamines. The second step proceeds easily at 50 °C or higher, and sodium hydroxide is successfully employed as base, though any base can be used.

The reaction of the keto acids with 4-hydroxydiphenylamines (**75**; R = H) gives directly the fluoran compounds (**77**), not via phthalide intermediate. The yields, however, are much lower than those using 4-alkoxydiphenylamines.

In addition, the reaction with 4-methoxydiphenylamines having a *t*-butyl group on the anisole moiety does not give the corresponding fluoran compounds, because the *t*-butyl group is liable to eliminate in sulfuric acid. For example, the reaction of 5-*t*-butyl-4-methoxy-2-methyldiphenylamine (**78**; R = *t*-C₄H₉) with keto acid gives the same product derived from 4-methoxy-2-methyldiphenylamine (**78**; R = H).



(78)

Table 6 shows melting points of various 2'-anilino-6'-aminofluorans (77).

Some fluoran compounds in Table 6 are found to form adducts with solvent. For example, when 6'-diethylamino-2'-(2,4-dimethylanilino)-3'-methylfluoran (77e) is recrystallized from toluene, it forms an adduct, mp 137–139°C, having 0.5mol of toluene of crystallization per mol of the fluoran; the toluene of crystallization liberates on treatment with boiling n-hexane or isopropanol or on heating in vacuo. 2'-Anilino-6'-(N-cyclohexyl-N-methylamino)-3'-methylfluoran (77c) forms an adduct with acetone⁶⁹ having a melting point of 133–135 °C. 2'-Anilino-6'-(N-ethyl-N-isobutylamino)-3'-methylfluoran (77g) forms adducts with acetone⁶⁹ and 2-butanone⁶⁹ having a melting point of 139–141 and 128–129 °C, respectively. 2'-Anilino-6'-(N-ethyl-4-methylanilino)-3'-methylfluoran (75) also forms an adduct with acetone⁶⁹ having a melting point of 152–153 °C.

Preparation of 2'-Anilino-6'-diethylamino-3'-methylfluoran (77d). To a solution of 2-(4-diethylamino-2-hydroxybenzoyl)benzoic acid (0.1 mol) in 98% sulfuric acid (150 g) was added 4-methoxy-2-methyldiphenylamine (0.1 mol) in limited amounts, while the temperature was maintained to not rise above 30 °C. The resulting mixture was stirred at room temperature for 20 h, and poured into ice water (1000 ml). The precipitate was filtered off, washed with water, and then refluxed with a mixture of toluene (400 ml) and 20% aqueous sodium hydroxide (150 g) for 1 h. The toluene layer was separated, washed with hot water, and concentrated to leave ca. 100ml of toluene. The residue was then refluxed with methanol (100 ml) for 1 h. After being cooled, the precipitate is filtered off, washed with methanol, and dried to give 2'-anilino-6'-diethylamino-3'-methylfluoran in 90% yield as an off-white powder, mp 197–198 °C.

Preparation of 6'-Diethylamino-2'-(2,4-dimethylanilino)-3'-methylfluoran (77e). To a solution of 2-(4-diethylamino-2-hydroxybenzoyl)benzoic acid (0.1 mol) in 98% sulfuric acid (150 g) was added 4-methoxy-2,2',4'-trimethyldiphenylamine (0.1 mol) in limited amounts, while the temperature

Table 6. Melting Points of 2'-Anilino-6'-aminofluorans (77)

77	R ¹	R ²	R ³	R ⁴	R ⁵	mp °C
a	CH ₃	CH ₃	CH ₃	H	H	202–203
b	CH ₃	<i>n</i> -C ₃ H ₇	CH ₃	H	H	175–178
c	CH ₃	<i>c</i> -C ₆ H ₁₁	CH ₃	H	H	206–208
d	CH ₃	C ₂ H ₅	CH ₃	H	H	197–198
e	C ₂ H ₅	C ₂ H ₅	CH ₃	H	2,4-(CH ₃) ₂	170–172
f	C ₂ H ₅	C ₂ H ₅	CH ₃	H	2,6-(CH ₃) ₂	163–164
g	C ₂ H ₅	<i>i</i> -C ₄ H ₉	CH ₃	H	H	151–154
h	C ₂ H ₅	<i>i</i> -C ₅ H ₁₁	CH ₃	H	H	164–167
i	C ₂ H ₅	C ₂ H ₅ OC ₃ H ₆	CH ₃	H	H	151–153
j	C ₂ H ₅	4-CH ₃ C ₆ H ₄	CH ₃	H	H	207–209
k	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	CH ₃	H	H	180–182
l	—(CH ₂) ₄ —		CH ₃	H	H	216–218
m	C ₂ H ₅	C ₂ H ₅	CH ₃ O	H	H	174–175
n	C ₂ H ₅	C ₂ H ₅	Cl	H	H	179–180
o	C ₂ H ₅	C ₂ H ₅	H	H	2-Cl	221–223
p	C ₂ H ₅	C ₂ H ₅	H	H	3-CF ₃	180–181
q	C ₂ H ₅	C ₂ H ₅	H	H	4-CH ₃	212–216
r	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	H	H	2-Cl	185–188
s	C ₂ H ₅	C ₂ H ₅	H	CH ₃	H	158–160
t	C ₂ H ₅	C ₂ H ₅	H	CH ₃	3-CF ₃	146–148
u	C ₂ H ₅	C ₂ H ₅	H	CH ₃	4-CH ₃	171–172
v	C ₂ H ₅	C ₂ H ₅	H	C ₂ H ₅	H	142–143

was maintained to not rise above 30°C. The resulting mixture was stirred at room temperature for 20h, and poured into ice water (1000ml). The precipitate was filtered off, washed with water, and then refluxed with a mixture of toluene (400 ml) and 20% aqueous sodium hydroxide (150 g) for 1 h. The toluene layer was separated, washed with hot water, and concentrated to leave ca. 100 mL of toluene. After being cooled, the precipitate was filtered off, and dried to give an adduct with toluene. The adduct was then refluxed with isopropanol (100 ml) for 1 h. After being cooled, the solid was filtered off, and dried to give 6'-diethylamino-2'-(2,4-dimethylanilino)-3'-methylfluoran in 83% yield as an off-white powder, mp 170–172 °C.

*Preparation of 2'-Anilino-6'-di-*n*-butylamino-3'-methylfluoran (77k).* To a solution of 2-(4-di-*n*-butylamino-2-hydroxybenzoyl)benzoic acid (0.1 mol) in 98% sulfuric acid (150 g) was added 4-methoxy-2-methyldiphenylamine (0.1 mol) in limited amounts, while the temperature was maintained to not rise above 30°C. The resulting mixture was stirred at room temperature for 20h, and poured into ice water (1000ml). The precipitate was filtered off, washed with water, and then refluxed with a mixture of toluene (400 ml) and 20% aqueous sodium hydroxide (150 g) for 1 h. The toluene layer was separated, washed with hot water, and concentrated to leave ca. 100 ml of toluene. After being cooled, the precipitate was filtered off, and dried to give 2'-anilino-6'-di-*n*-butylamino-3'-methylfluoran in 90% yield as a white powder, mp 180–182°C.

6.3.3. Reaction of Keto Acids with 3-Alkoxydiphenylamines

The reaction of keto acids (**79**) having no amino group with 3-alkoxydiphenylamines (**80**) is used to synthesize 3'-anilino fluorans (**81**), especially near-infrared-absorbing fluoran compounds (Eq. 6).

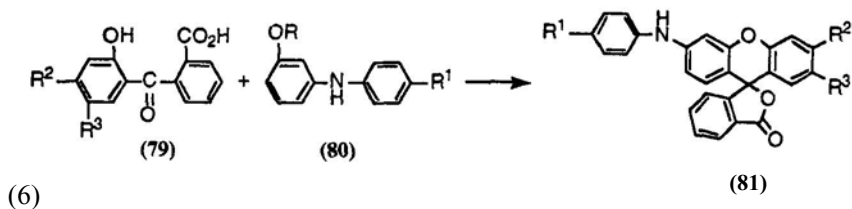
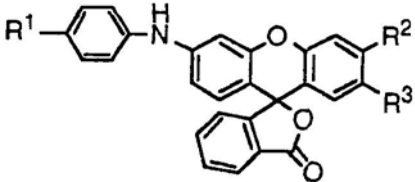


Table 7 shows melting points of a few near-infrared-absorbing fluoran compounds (**81**) thus prepared.

Preparation of 6'-[4-(4-Anilinoanilino)anilino]-2'-chloro-3'-methylfluoran (81a). To concentrated sulfuric acid (10 g) was added 2-(5-chloro-2-hydroxy-4-methylbenzoyl)benzoic acid (3.4 mmol) followed by 4-anilino-4'-(3-methoxyanilino)diphenylamine (2.6 mmol). The mixture was stirred at room temperature for 24h, and poured into ice water (100ml). The precipitate was filtered off, washed with water, and then refluxed with a mixture of toluene (150 ml) and sodium hydroxide (20 g) dissolved in water (150ml) for 1 h. The toluene layer was separated, washed with hot water, and concentrated. The residue was then column chromatographed on silica gel to give 6'-[4-(4-anilinoanilino)anilino]-2'-chloro-3'-methylfluoran in 43% yield as a grayish white powder, mp 202–203 °C.

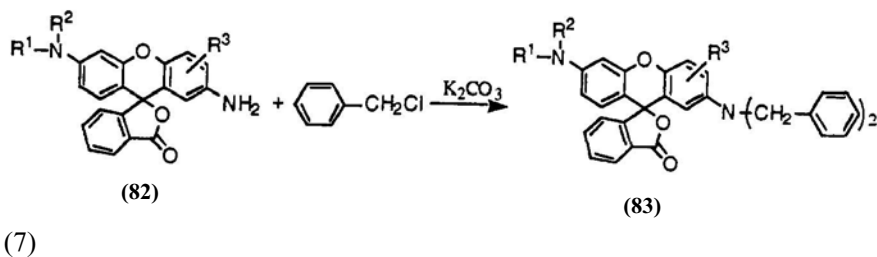
Table 7. Melting Points of NIR-Absorbing Fluoran Compounds (81)

				
81	R ¹	R ²	R ³	mp °C
a	4-C ₆ H ₅ NHC ₆ H ₄ NH	CH ₃	Cl	202–203
b	4-C ₆ H ₅ NHC ₆ H ₄ NH	H	CH ₃	133–136
c	4-(CH ₃) ₂ C ₆ H ₄ NH	H	CH ₃	199–202

6.3.4. Reaction of 2'-Aminofluorans with Aralkyl Halides

The reaction of 2'-aminofluorans with aralkyl halides is solely used to prepare 2'-diaralkylaminofluorans developing red or green colors.

Thus, 2'-aminofluorans (82) reacts with benzyl chloride in organic solvent such as isopropanol or toluene at reflux in the presence of potassium carbonate or sodium carbonate to give 2'-dibenzylaminofluorans (83) in excellent yield. (Eq. 7).



Besides benzyl chloride, methyl- and/or chlorine-substituted benzyl chlorides, phenethyl chloride, etc. are also successfully employed to give 2'-diaralkylaminofluorans in excellent yield. However, aryl halides such as chlorobenzene and bromobenzene hardly enable the reaction, though aryl iodides such as iodobenzene give 2'-diarylaminofluorans in low yield.

Table 8 shows melting points of 2'-dibenzylaminofluorans (83).

Table 8. Melting Points of 2'-Dibenzylaminofluorans (**83**)

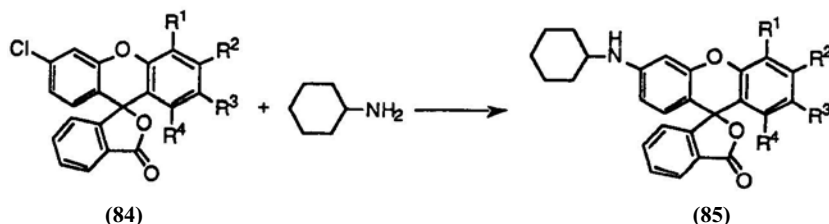
83	R ¹	R ²	R ³	mp °C
a	C ₂ H ₅	C ₂ H ₅	H	173–174
b	C ₂ H ₅	C ₂ H ₅	3'-CH ₃	152–155
c	C ₂ H ₅	C ₂ H ₅	3'-C ₂ H ₅	173–175
d	C ₂ H ₅	C ₂ H ₅	4'-Cl	165–166
e	C ₂ H ₅	C ₂ H ₅	4'-CH ₃ O	184–186
f	—(CH ₂) ₄ —		3'-CH ₃	213–215
g	C ₂ H ₅	4-CH ₃ C ₆ H ₄	4'-CH ₃ O	162–165

Preparation of 2'-Dibenzylamino-6'-diethylaminofluoran (83a). A mixture of 2'-amino-6'-diethylaminofluoran (0.1 mol), benzyl chloride (0.4 mol), and potassium carbonate (0.2 mol) in isopropanol (100 ml) was stirred under reflux until the reaction was complete: the reaction progress was easily monitored by TLC. Then, isopropanol was distilled out, and toluene (400ml) and water (100ml) were added. After refluxing for 1 h, the toluene layer was separated, washed with hot water, and concentrated. The residue was refluxed with methanol (200ml) for 1 h. After being cooled, the precipitate was filtered off, washed with methanol, and dried to give 2'-dibenzylamino-6'-diethylaminofluoran in 85% yield as a pale green crystalline powder, mp 173–174 °C.

6.3.5. Reaction of 3'-Chlorofluorans with Amines

3'-Chlorofluorans react with a wide variety of primary amines such as alkylamines, cycloalkylamines, aralkylamines, and arylamines, as well as cyclic secondary amines such as piperidine, morpholine, etc., to prepare 3'-aminofluorans.

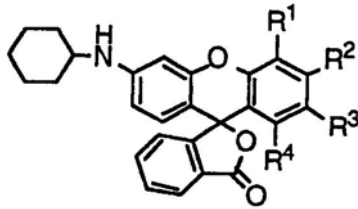
The typical example is, however, the reaction of 3'-chlorofluoran (**84**) with cyclohexylamine to give 3'-cyclohexylaminofluorans (**85**) (Eq. 8).



The reaction is successfully carried out at 180–220°C in the presence of zinc chloride and zinc oxide. When 3',6'-dichlorofluoran (**84**; R¹ R³, R⁴ = H, R² = Cl) is employed, the reaction gives 3'-chloro-6'-cyclohexylaminofluoran (**85**; R¹ R³, R⁴ = H, R² = Cl) together with 3',6'-dicyclohexylaminofluoran (**85**; R¹ R³, R⁴ = H, R² = *c*-C₆H₁₁NH). On the other hand, 2',6'-dichlorofluoran (**84**; R¹ R², R⁴ = H, R³ = Cl) gives solely 2'-chloro-6'-cyclohexylaminofluoran (**85**; R¹ R², R⁴ = H, R³ = Cl) because of low reactivity of chlorine at 2'-position. 2'-Bromo-6'-chlorofluoran (**84**; R¹ R², R⁴ = H, R³ = Br) also gives 2'-bromo-6'-cyclohexylaminofluoran (**85**; R¹ R², R⁴ = H, R³ = Br) in high selectivity.

Table 9 shows melting points of 3'-cyclohexylaminofluorans (**85**).

Table 9. Melting Points of 3'-Cyclohexylaminofluorans (**85**)

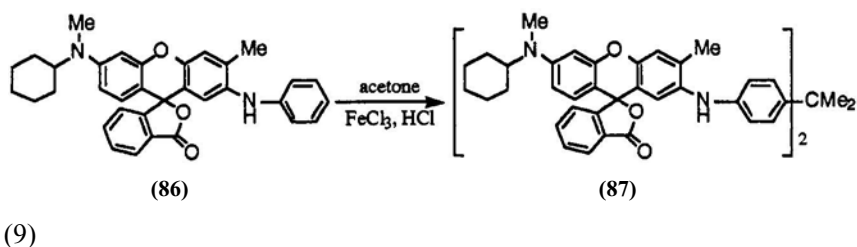


85	R ¹	R ²	R ³	R ⁴	mp °C
a	H	Cl	H	H	178–181
b	H	H	Br	H	235–237
c	H	H	Cl	H	207–209
d	H	H	CH ₃	H	137–140
e	H	CH ₃	Cl	CH ₃	186–188
f	—(CH=CH) ₂	H	H	H	168–170
g	H	H	—(CH=CH) ₂ —	—	222–224

Preparation of 3'-Chloro-6'-cyclohexylaminofluoran (85a). A mixture of 3',6'-dichlorofluoran (0.1 mol), cyclohexylamine hydrochloride (0.15 mol), zinc chloride (0.3 mol), and zinc oxide (0.2 mol) was fused at 190–200 °C for 4 h. After being cooled, the solidified mixture was powdered, heated with 4% hydrochloric acid (1000 ml) to dissolve zinc chloride, and filtered. Then, the filter cake was refluxed with a mixture of toluene (400ml) and 5% aqueous sodium hydroxide (100 ml) for 1 h. The toluene layer was separated, washed with hot water, and concentrated. The residue was refluxed with methanol (200ml) for 1 h. After being cooled, the precipitate was filtered off, washed with methanol, and dried to give 3'-chloro-6'-cyclohexylaminofluoran in 60% yield as an off-white powder, mp 178–181 °C.

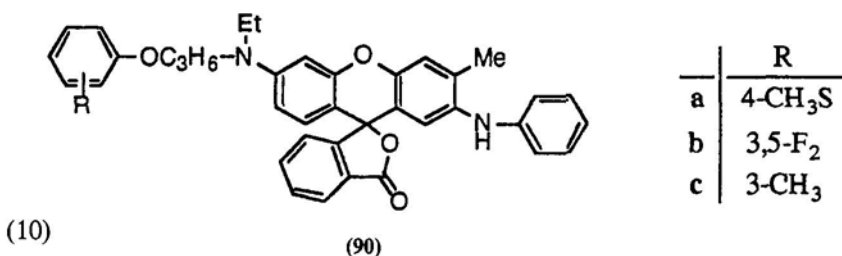
6.3.6. Other Reactions

Treatment of 2'-anilinofluorans with ketones such as acetone or 2-butanone in hydrochloric acid in the presence of iron(III) chloride gives 4,4'-alkylidenebis(*N*-fluoran-2-ylaniline)s. Thus, 2'-anilino-6'-(*N*-cyclohexyl-*N*-methylamino)-3'-methylfluoran, (86) is treated with acetone in hydrochloric acid in the presence of iron(III) chloride to give 2,2-bis(4-[6'-(*N*-cyclohexyl-*N*-methylamino)-3'-methylfluoran-2'-ylamino]phenyl)propane (87)⁶⁰ (Eq. 9).

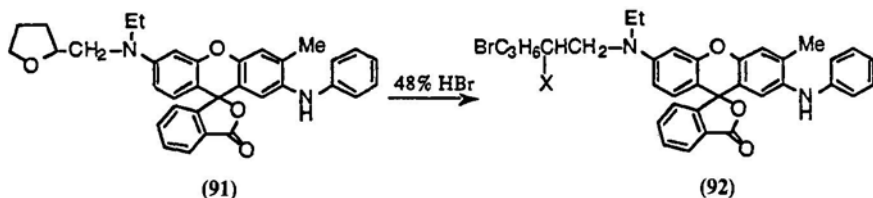


Treating 2'-anilino-6'-[*N*-ethyl-*N*-(3-methoxypropyl)amino]-3'-methylfluoran (88) with 48% hydrobromic acid in the presence of concentrated sulfuric acid at 110–115 °C gives 2'-anilino-6'-[*N*-(3'-bromopropyl)-*N*-ethylamino]-3'-methylfluoran (89)⁷⁰ in excellent yield (Eq. 10).

The fluoran 89 reacts with phenols in *N,N*-dimethylacetamide in the presence of potassium carbonate to give 2'-anilino-6'-[*N*-ethyl-*N*-[3-(4-methylthiophenoxy)propyl]amino]-3'-methylfluoran (90a),⁷¹ 2'-anilino-6'-[*N*-ethyl-*N*-[3-(3,5-difluorophenoxy)propyl]amino]-3'-methylfluoran (90b),⁷¹ 2'-anilino-6'-[*N*-ethyl-*N*-[3-(3-methylphenoxy)propyl]amino]-3'-methylfluoran (90c),⁷¹ etc. in excellent yield.



Tetrahydrofuran moiety of 2'-anilino-6'-(*N*-ethyl-*N*-tetrahydrofurfurylamino)-3'-methylfluoran (**91**) can be hydrolyzed with 48% hydrobromic acid in sulfolane to give 2'-anilino-6'-[*N*-(5-bromo-2-hydroxypentyl)-*N*-ethylamino]-3'-methylfluoran (**92**; X = OH)⁷² and 2'-anilino-6'-[*N*-(2,5-dibromopentyl)-*N*-ethylamino]-3'-methylfluoran (**92**; X = Br)⁷² at 70–90 °C and 100 °C, respectively (Eq. 11).



(11)

*Preparation of 2,2-Bis(4-[6'-(*N*-cyclohexyl-*N*-methylamino)-3'-methylfluoran-2'-ylamino]phenyl)propane (87).* To a solution of 2'-anilino-6'-(*N*-cyclohexyl-*N*-methylamino)-3'-methylfluoran (0.1 mol) in 250 ml of acetone heated at 60°C was added dropwise 300ml of 35% hydrochloric acid over a period of 30min, and stirring was continued for 30min. To this, after being cooled to room temperature, was added iron(III) chloride (0.04 mol). The resulting mixture was stirred at room temperature overnight, diluted with 3 liters of water, and neutralized by sodium bicarbonate. The precipi-

tate was filtered off, and recrystallized from toluene in the usual manner to give 2,2-bis{4-[6'-(*N*-cyclohexyl-*N*-methylamino)-3'-methylfluoran-2'-yl-amino]phenyl}propane in 35% yield as a white powder, mp 237–239 °C.

Preparation of 2'-Anilino-6'-[N-(3-bromopropyl)-N-ethylamino]-3'-methylfluoran (89). To a mixture of 2'-anilino-6'-[*N*-ethyl-*N*-(3-methoxypropyl)amino]-3'-methylfluoran (0.1 mol) and 48% hydrobromic acid (150 ml) was added dropwise concentrated sulfuric acid (20 ml) with vigorous stirring. Then, the resulting mixture was stirred at 110–115 °C for 1 h, poured into ice water (1000ml), and made alkaline by aqueous sodium hydroxide. The pale violet precipitate was filtered off, and recrystallized from ethyl acetate–isopropanol to give 2'-anilino-6'-[*N*-(3-bromopropyl)-*N*-ethylamino]-3'-methylfluoran in 96% yield, mp 160–162 °C.

*Preparation of 2'-Anilino-6'-{N-ethyl-*N*-[3-(4-methylthiophenoxy)propyl]amino}-3'-methylfluoran (90a).* A mixture of 2'-anilino-6'-[*N*-(3-bromopropyl)-*N*-ethylamino]-3'-methylfluoran (0.1 mol), 4-(methylthio)phenol (0.1 mol), and potassium carbonate (0.14 mol) in *N,N*-dimethylacetamide (100ml) was stirred at 85 °C for 1 h. The reaction mixture was poured into ice water (500ml). The precipitate was filtered off, and recrystallized from ethanol to give 2'-anilino-6'-{*N*-ethyl-*N*-[3-(4-methylthiophenoxy)propyl]amino}-3'-methylfluoran in 91% yield, mp 187–189 °C.

6.4. APPLICATIONS OF FLUORAN COMPOUNDS

Fluoran compounds have been used in a variety of fields. These include sublimation transfer printing, thermoindicator, printed circuits, writing materials, textile finishing, etc., though recording papers, i.e., carbonless copying paper and thermosensitive recording paper, are extraordinarily large in volume. This section describes carbonless copying paper and thermosensitive recording paper.

6.4.1. Carbonless Copying Paper

6.4.1.1. Background

In 1954, the National Cash Register Company introduced a new copying system, i.e., carbonless copying paper, by which multiple copies were realized without using traditional carbon paper. Since then, there have been numerous changes and improvements, though the original system is still the technological basis for the current carbonless copying papers.

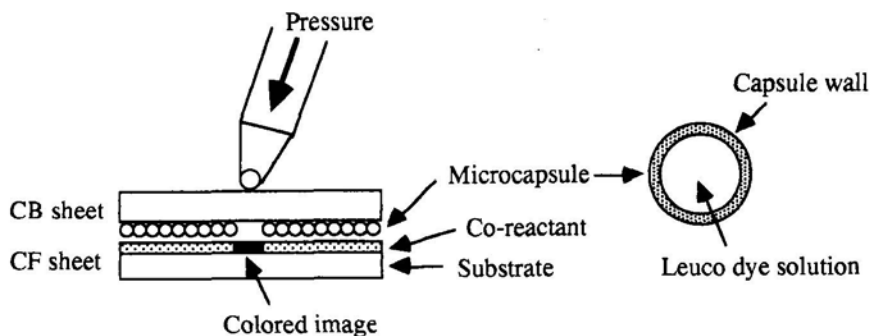


Figure 6.6. Structure of carbonless copying paper.

Carbonless copying paper basically consists of a two-sheet system; the top and bottom sheet are termed the CB and CF sheet, respectively. A cross-sectional view of the structure is shown in Figure 6.6.

The CB sheet is coated on the back with microcapsules 5 to 10 μm in diameter, in which leuco dye solution in a nonvolatile solvent is contained. The CF sheet is coated on the front with an acidic coreactant such as reactive clay, zinc salt of salicylic acid derivatives, zinc-modified phenolic resin, etc. On the application of pressure, the microcapsule is ruptured in the area delineated by the pressure pattern, and the leuco dye solution is thereby transferred to the CB sheet to bring about a color-forming reaction with acidic coreactant resulting in a distinct image on the surface of the CF sheet. By inserting a middle sheet (or sheets) called the CFB sheet, which is coated on the front and back with acidic coreactant and microcapsules, respectively, multiple copies can be obtained.

Today, the total consumption of carbonless copying paper worldwide is estimated to be 2 million tons. The major use for carbonless copying paper is in continuous business forms processed by computer.

6.4.1.2. Preparation of Carbonless Copying Paper

A leuco dye(s) solution in a nonvolatile solvent is encapsulated in microcapsules 5–10 μm in diameter, and after addition of latex and wheat starch, coated (at about 5 g/m^2 as dry solid) on a substrate such as paper, synthetic paper, or plastic film, and dried to give the CB sheet.

The solvent should have high solvability with no or very low odor. Two examples are SAS-296 (diarylalkane, Nippon Petroleum Chemicals) and KMC-113 (dialkyl-naphthalene, Kureha Chemicals). Latex is used as binder. Wheat starch functions as a stilt preventing the rupture of microcapsules

from careless or undesirable pressure. It should, therefore, be a little larger than the microcapsule. A brief explanation of the microcapsules is given in the next section.

The CF sheet is prepared by coating an acidic coreactant such as naturally occurring reactive clay, zinc salt of salicylic acid derivatives and zinc modified phenolic resin.

Reactive clay is used today principally in European countries, though it was once used worldwide. Zinc salt of salicylic acid derivatives and zinc-modified phenolic resin are used in Japan and the United States, respectively. The synthetic coreactants have a special feature giving stable recorded images.

6.4.1.3. Microcapsule

Microencapsulation is a revolutionary technology enabling liquids to be treated as solids. The technology was first used to produce carbonless copying paper, but today it is widely used in a number of industrial fields such as medicine, agricultural chemicals, thermochromic materials, cosmetics, and toiletries.

The original microcapsule was produced by a complex coacervation between gelatin and gum arabic. Gelatin changes its charge depending on pH value; it has negative and positive charges at pH values above and below its isoelectric point, respectively. On the other hand, gum arabic has a negative charge regardless of pH value. The colloidal mixture of gelatin and gum arabic, therefore, brings about a neutralizing reaction at pH values below the isoelectric point of gelatin, resulting in polymerization.

The typical microencapsulation process via complex coacervation is illustrated in Figure 6.7.

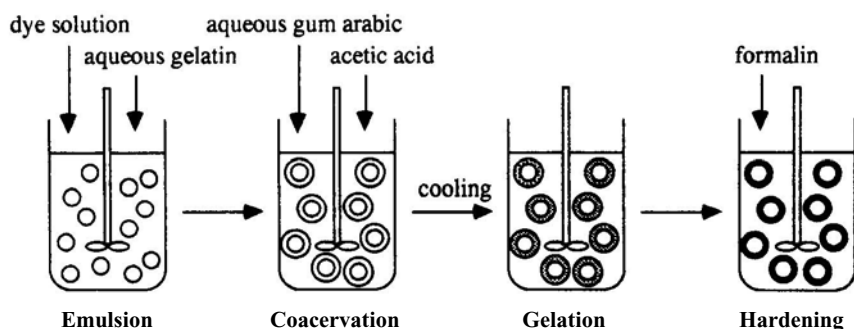


Figure 6.7. Microencapsulation by complex coacervation.

A leuco dye solution (3–5%, 100 g) is emulsified in an aqueous solution of gelatin (5%, 100 g) at 50 °C until the droplet is 5 to 10 μm in diameter. The droplet size is governed by the rate of agitation. Once the appropriate droplet size is achieved, an aqueous solution of gum arabic (5%, 100g) is added. The mixture is then diluted with water (50°C, 200ml), and the pH is adjusted to 4–5 with acetic acid to permit coacervation resulting in deposition of a thin film of liquid polymer on the core of the droplet of leuco dye solution. The liquid polymer is gelled by cooling below 10 °C, and then hardened with formaldehyde. The mixture is finally adjusted to pH 9 to give microcapsules containing leuco dye solution.

Recently, many synthetic polymers such as urea/formalin resin, melamine/formalin resin, polyester, and polyurethane have been widely used as the wall material for the microcapsule, though the gelatin microcapsule is still used. Microcapsules using a synthetic polymer wall have several advantages over those using a gelatin wall: (1) the preparation process is simple, (2) the size of the microcapsules is well balanced, (3) the microcapsule concentration can be increased twofold or more and (4) the microcapsules have a high resistance to water and many chemicals. Synthetic microcapsules are prepared by interfacial polymerization or *in situ* polymerization.

6.4.2. Thermosensitive Recording Paper

6.4.2.1. Background

Thermosensitive recording paper was introduced by the National Cash Register Company in 1968. The chemistry employed is essentially the same as that for carbonless papers, i.e., color-formation reaction between leuco dye and coreactant, though thermosensitive recording papers require certain unique leuco dyes and coreactants. Thermosensitive recording papers generally consist of a single-sheet system in contrast with the two-sheet system for carbonless copying papers. The surface of the sheet has a thermosensitive layer comprising leuco dye and coreactant as essential color-forming components together with several additives. A cross-sectional view of the structure is shown in Figure 6.8.

The thermosensitive recording paper itself is white like a plain sheet of paper. With the application of heat by means of a thermal pen or thermal head, the color-forming components in the thermosensitive layer are brought into reactive contact in the area delineated by the heat pattern resulting in a distinct image.

The color-forming mechanism is simple and direct, only requiring heat application, and the recording equipment is free from maintenance, highly reliable, and less expensive. Thermosensitive recording papers can be used

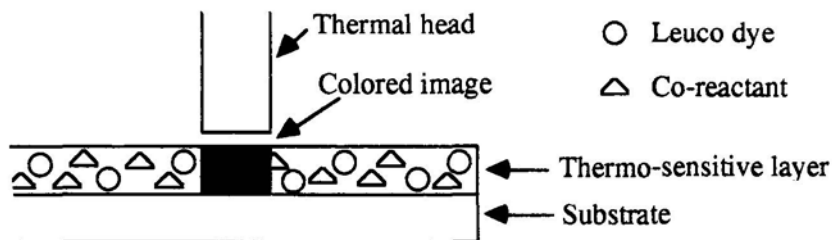


Figure 6.8. Structure of thermosensitive recording paper.

for various purposes. These include facsimile, medical instruments such as electrocardiograph, spectrophotometer, printer, and video printer. Today, the demand of thermosensitive recording paper for facsimile is 70% or more in total consumption of 300,000 tons worldwide.

6.4.2.2. Preparation of Thermosensitive Recording Paper

Leuco dye and coreactant are individually milled in an aqueous solution of binder such as poly(vinyl alcohol) or hydroxyethylcellulose by means of an attrition or sand mill until the particle size of the solid materials is about 1 μm or less in diameter. Smaller particles provide superior performance.

These dispersions thus obtained are mixed together, and after the introduction of other additives, coated (at about 5–10 g/m^2 as dry solid) on a substrate such as paper, synthetic paper, or plastic film, dried, and calendered to give thermosensitive recording paper.

As for leuco dyes, black developing fluoran compounds are exclusively employed. They should be carefully selected to give thermosensitive recording papers of high whiteness and high image stability. Consequently, 2'-anilino-6'-di-*n*-butylamino-3'-methylfluoran (**93**; $\text{R}^1, \text{R}^2 = n\text{-C}_4\text{H}_9$) and 2'-anilino-6'-(*N*-ethyl-*N*-isopentylamino)-3'-methylfluoran (**93**; $\text{R}^1 = \text{C}_2\text{H}_5$, $\text{R}^2 = i\text{-C}_5\text{H}_{11}$) are generally used.

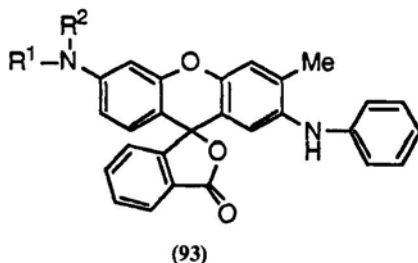
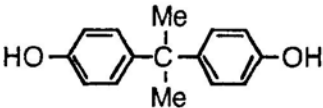
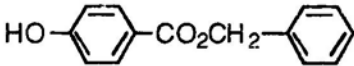
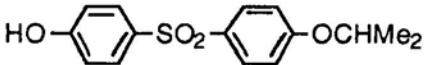
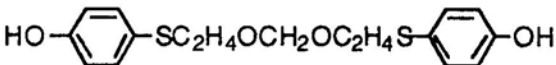
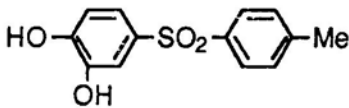


Table 10. Coreactants for Thermosensitive Recording Paper

Compound	mp°C	Ref.
	156	73
	110	74
	130	75
	109	76
	179	77

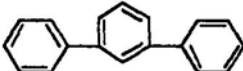
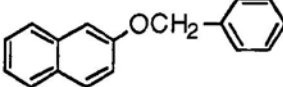
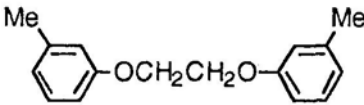
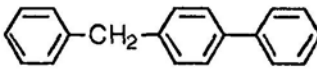
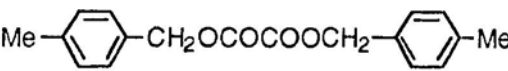
Coreactants have a substantial influence on whiteness, sensitivity, and image stability of thermosensitive recording paper. All of the coreactants used in thermosensitive recording papers are phenol derivatives, and representative examples are shown in Table 10.

2,2-Bis(4-hydroxyphenyl)propane (Bisphenol A) has been most widely used, because it gives a fairly stable image and is low in price. In the past, it presented a problem for high-speed recording because of its high melting point, which has, however, been solved by using suitable sensitizers. Benzyl 4-hydroxybenzoate and 1,7-bis(4-hydroxyphenylthio)-3,5-dioxaheptane are suitable for high-speed recording without sensitizer, but inferior to Bisphenol A in image stability. 4-Hydroxy-4'-isopropoxydiphenyl sulfone has received attention recently due to its image stability. 3,4-Dihydroxy-4'-methylphenyl sulfone is solely used in prepaid cards.

In addition to leuco dye and coreactant, many additives such as sensitizer, stabilizer, filler, lubricant, antipressure agent, etc. are used in the thermosensitive layer.

Coreactants having a higher melting point cannot provide enough image intensity on high-speed or low-energy recording. Thus, aromatic compounds having a melting point of about 100°C are employed as

Table 11. Sensitizers for Thermosensitive Recording Paper

Compound	mp°C	Ref.
	89	78
	101	79
	98	80
	86	81
	102	82

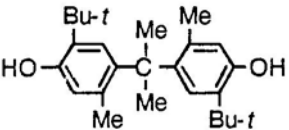
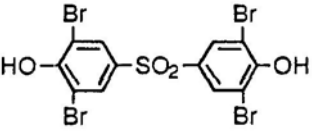
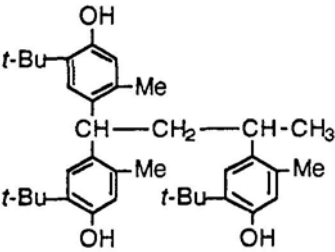
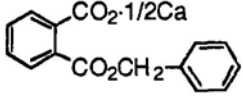
sensitizer, which makes it possible to lower the developing temperature by forming a eutectic mixture, whereas thermosensitive recording papers using lower-melting coreactants such as benzyl 4-hydroxybenzoate are of high sensitivity without sensitizer. Table 11 shows representative sensitizers.

The recorded images are subject to fade on long storage or under hot humidity. To counter this, hindered phenol derivatives are employed as stabilizer. It is essential to use a stabilizer when benzyl 4-hydroxybenzoate is a coreactant. Benzyl 4-hydroxybenzoate has a high crystallization resulting in bleeding from the recorded image. Addition of stabilizer is effective in preventing such bleeding. In addition, aromatic carboxylic acid metal salts such as calcium benzyl phthalate are effective stabilizers for plasticizer and oil. Table 12 shows typical stabilizers.

White pigments such as calcium carbonate, aluminum hydroxide, silica, kaolin, or urea-formaldehyderesin are used as filler. The filler functions as an absorbent of melted components to prevent their adhesion on the thermal head. Thus, the filler is required to be high in oil absorption and not to wear the thermal head.

Metallic soaps such as zinc stearate or calcium stearate are used as lubricant, which reduces the friction coefficient of the surface of the thermosensitive layer resulting in smooth running on recording machines.

Table 12. Stabilizers for Thermosensitive Recording Paper

Compound	Ref.
 Chemical structure of a bisphenol A derivative. It consists of two phenolic rings connected by a central carbon atom. Each ring has a hydroxyl group (HO-) at the para position and a tert-butyl group (Bu-t) at the 2-position. The central carbon is also bonded to two methyl groups (Me).	83
 Chemical structure of a bisphenol A derivative. It consists of two phenolic rings connected by a sulfone group (-SO₂-). Each ring has a hydroxyl group (HO-) at the para position and two bromine atoms (Br) at the 2 and 6 positions.	84
 Chemical structure of a bisphenol A derivative. It consists of two phenolic rings connected by a central carbon atom. Each ring has a hydroxyl group (OH) at the para position, a tert-butyl group (t-Bu) at the 2-position, and a methyl group (Me) at the 6-position. The central carbon is also bonded to two methyl groups (Me).	85
 Chemical structure of a bisphenol A derivative. It consists of two phenolic rings connected by a carbonate group (-CO₂-). Each ring has a hydroxyl group (OH) at the para position and a methyl group (Me) at the 6-position.	86

The smoothness of the surface of the thermosensitive layer has considerable influence on image intensity and image reproducibility. This is achieved by calendering of high line pressure. So, paraffin waxes are used as antipressure agent in order to prevent undesirable coloring on calendering.

6.5. REFERENCES

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7

The Chemistry of Tetrazolium Salts

DANIEL S. DANIEL

7.1. INTRODUCTION

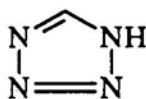
Tetrazolium salts are an important class of leuco dyes that have found a wide range of applications. They are unique among the synthetic leuco dyes in that the colored form of the dye is the reduced form rather than the oxidized form. There are at least three extensive reviews on tetrazolium salts and the corresponding formazan dyes¹⁻³ and one textbook.⁹⁶ This chapter will describe some recent developments as well as some of the material covered in these reviews.

Tetrazolium salts to a large extent are prepared from the corresponding formazans and to a lesser extent from tetrazoles. Therefore, synthetic methods for both formazans and tetrazoles will be discussed. Also discussed will be some properties of formazan dyes that influence the choice of the tetrazolium salt for any particular application.

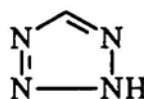
7.2. NOMENCLATURE AND RING NUMBERING SYSTEM

Tetrazolium salts are derivatives of the ¹H-tetrazole (**1**) or 2H-tetrazole (**2**). The CA numbering systems for tetrazoliums and formazans are shown in **3** and **4**. It should be noted that the carbon atoms in **3** and **4** are

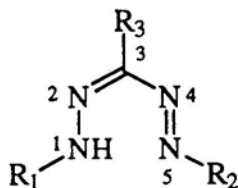
DANIEL S. DANIEL • Clinical Chemistry Research and Development, Johnson & Johnson Clinical Diagnostics, Rochester, New York 14650-2113.
Chemistry and Applications of Leuco Dyes, edited by Muthyala. Plenum Press, New York, 1997.



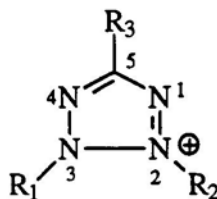
(1)



(2)



(3)



(4)

numbered 3 and 5, respectively. For example, where R_1 and R_2 are phenyls and R_3 is methyl, **3** is named 3-methyl-1,5-diphenylformazan, while the tetrazolium salt **4** is named 5-methyl-2,3-diphenyl-2*H*-tetrazolium. Some authors refer to the more common tetrazolium salts by trivial names, usually based on the color of the formazan obtained through reduction of the salt. These names have seldom been applied consistently and have caused some confusion.

7.3. SYNTHESIS OF TETRAZOLIUM SALTS

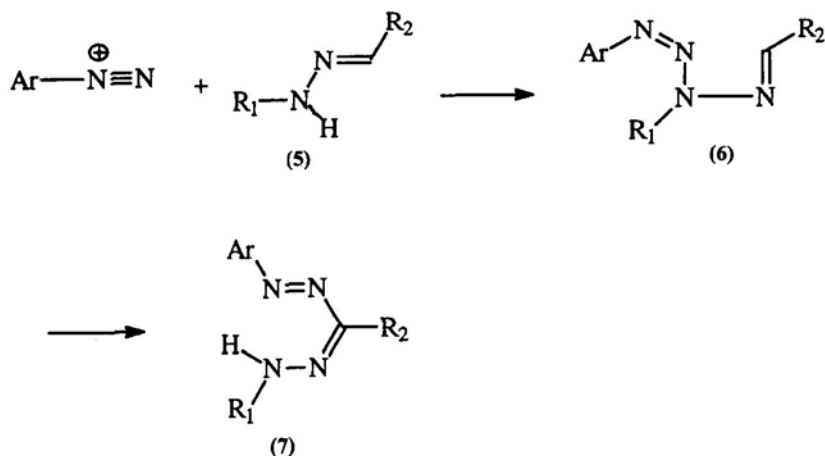
In general, tetrazolium salts are prepared by (a) oxidation of formazans and (b) alkylation of tetrazoles. Therefore, synthetic methods for formazans and tetrazoles are discussed first, followed by some direct and miscellaneous methods.

7.3.1. From Formazans

Synthetic methods for formazans have been reviewed.^{1,2}

7.3.1.1. From Diazonium Salts

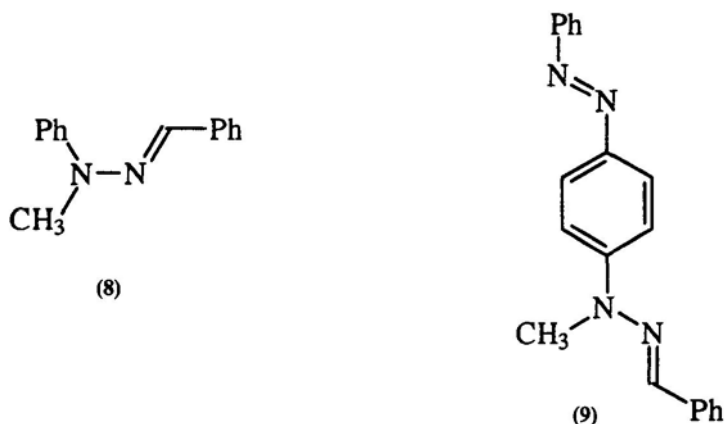
Electron-rich compounds such as hydrazones react with diazonium salts either at a nitrogen or at a carbon atom to yield formazans, either directly or through a subsequent rearrangement. The use of aldehyde

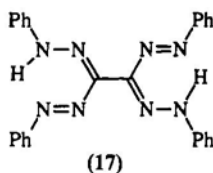
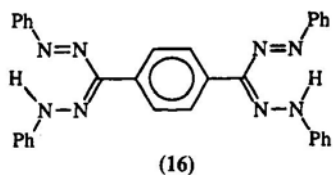
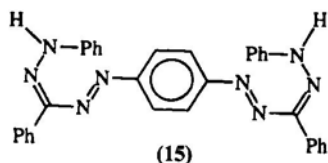


Scheme 1

hydrazones is the standard procedure for the preparation of triaryl formazans. Diazonium salts couple to the amine nitrogen in the hydrazone (5) with displacement of a hydrogen to give the intermediate (6) which then rearranges to the formazan (7) (Scheme 1).⁴⁻⁷

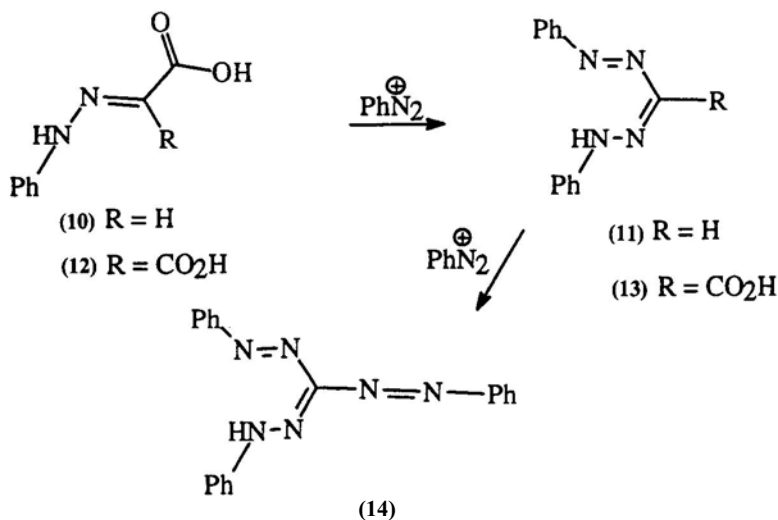
This mechanism is supported by the fact that a secondary hydrazone such as (8) yields the azohydrazone (9) rather than the formazan.⁸ Ketone hydrazones also yield azohydrazones. The coupling of hydrazones of glyoxylic acid (10) with diazonium salts is accompanied by decarboxylation to yield 3-unsubstituted formazans (11). Similarly, hydrazones of mesoxalic acid (12) yield formazans with a carboxyl group in position 3, e.g., 13 (Scheme 2).^{9,10} Both 11 and 13 can react with diazonium salts to yield the





azo-substituted formazan (**14**).⁴⁷⁴ This method is suitable for the preparation of bisformazans linked through nitrogen, e.g., **15**,¹²⁻¹⁶ or through the 3-carbon atom, e.g., **16** including the directly linked formazan (**17**).^{13,17-19} Table 1 illustrates the scope of this reaction.

Guanyl hydrazones (**18**) react with diazonium salts to yield a special class of formazans called guanazyls, e.g., **19** (Eq. 1).²⁰⁻²² The reaction is



Scheme 2

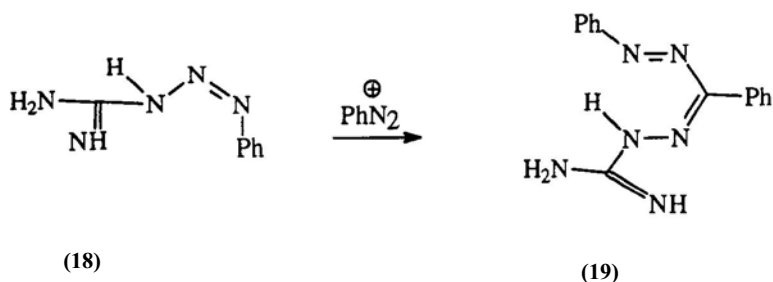
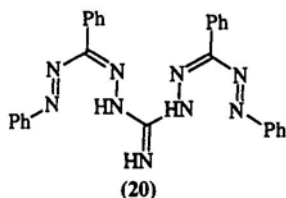


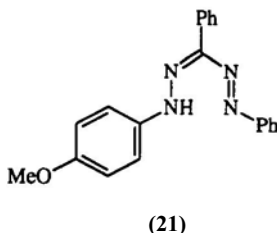
Table 1. Synthesis of Formazans (3) from Hydrazones

(3)				
R ₁	R ₂	R ₃	Yield (%)	Refs.
Ph	Ph	H	19	30, 37
Ph	Ph	CH ₃	44	54
Ph	Ph	Ph	23	4, 19, 51, 74, 102
Ph	4-HO ₂ C-C ₆ H ₄	CH ₃	100	449
Ph	4-H ₂ NSO ₂ -C ₆ H ₄	<i>n</i> -C ₁₁ H ₂₃	100	101
2-H ₃ C-C ₆ H ₄	1-Cl-C ₆ H ₄	CH ₂ CH ₂ OH	23	351
Ph	Ph	Glucose	33	365
Ph	α-C ₁₀ H ₇	Ph	80	299, 302, 341
Ph	4-(CH ₃) ₃ N ⁺ -C ₆ H ₄	2-HO-C ₆ H ₄	80	1
Ph	4-(CH ₃) ₃ N ⁺ -C ₆ H ₄	4-H ₃ CO ₂ -C ₆ H ₄	48	1
Ph	4-C ₆ H ₄ N=NC ₆ H ₅	CH ₃	28	643
Ph	4-C ₆ H ₄ N=NC ₆ H ₅	Ph	50	643
2-Pyridyl	2-Cl-C ₆ H ₄	2-Furyl	64	14
Ph	Ph	4-Pyridyl	46	340
Ph	Ph	CO ₂ Et	80	26, 30, 37
Ph	Ph	COCH ₃	70	26, 334, 366, 367
Ph	4-C ₆ H ₄ CH=CHPh	4-Pyridyl	39	340
Ph	Ph	1,4-Ethylene	90	12
Ph	4,4'-Biphenylene	CH ₃	36	48
Ph	4,4'-Biphenylene	Ph	76	15
Ph	4,4'-Biphenylene	2-Thienyl	33	15

quite versatile with 3-aryl substituents and can lead to bisguanazyls, e.g., **20**. However, 3-alkyl substituents limit the scope of the reaction.^{2,3-2,5}

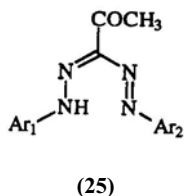


*Synthesis of 1-(4-Methoxyphenyl)-3,5-diphenylformazan (21).*⁵ A solution of 12.8 g of *p*-anisidine was dissolved in 50 ml of 6 M hydrochloric

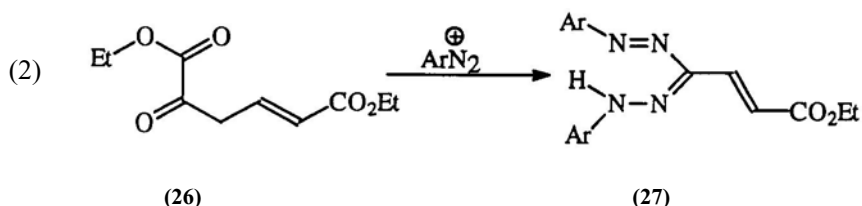


acid. The solution was cooled to -10°C and diazotized with a solution of 8.0g of sodium nitrite in 20ml of water. The diazonium salt solution was added in small portions (over 30min) to a stirred solution of 19.8 g of benzaldehyde phenylhydrazone in 110 ml of pyridine and 100 ml of ethanol at -10°C . The resulting solution (part suspension) was stirred for an additional hour at 0°C , then poured into 3 liters of water. The precipitated formazan was filtered and air dried. The crude formazan was recrystallized from 500 ml of ethanol yielding 17.0 g (52%) of product mp $149-150^{\circ}\text{C}$.

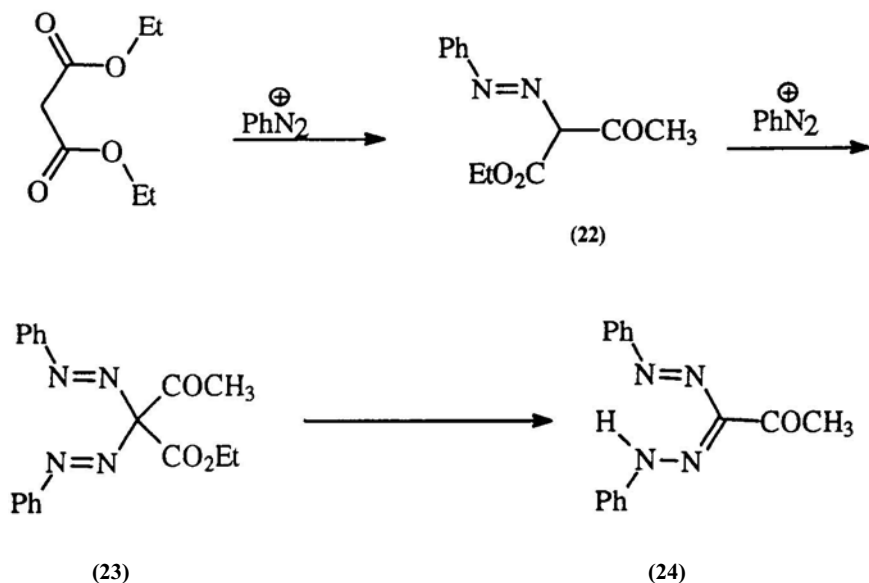
Diazonium salts add to active methylene compounds, for example ethyl acetoacetate, to form an intermediate azo compound (**22**), followed by the addition of a second diazonium salt (under more alkaline conditions) to yield the tetrazene (**23**) which then forms a 3-substituted formazan (**24**)¹⁰



through the loss of one of the electron-withdrawing substituent groups (usually an ester group) (Scheme 3). The isolation of the formazan (**13**) has also been reported.^{11,26} The relative displacement ability of a number of electron-withdrawing groups has been discussed.³⁵ The intermediate hydrazone (**22**) can be isolated under mild conditions and can be treated with a different diazonium salt to yield the unsymmetrical formazan (**25**).⁴⁵ This method is very useful for the preparation of 3-substituted formazans,

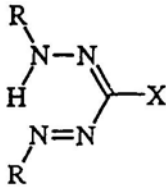


particularly when the starting aldehydes for hydrazone formation are not readily available. Unsaturated derivatives of reactive methylene compounds (**26**) can react with diazonium salts to form substituted formazans (**27**) (Eq. 2).⁴⁴ The case of potassium chloromalonate (**28**) is interesting in that the chloro-substituted formazan (**29**) is obtained with traces of the



Scheme3

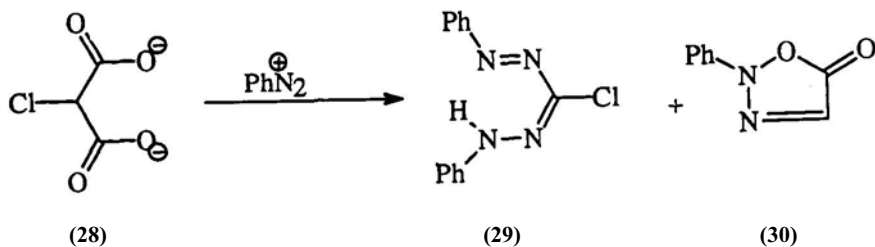
Table 2. Synthesis of Formazans from Methylene Compounds



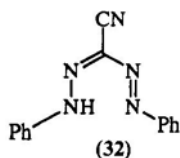
(31)

R	X	Yield (%)	Refs.
Ph	—N=NC ₆ H ₄	20	18, 30, 31
Ph	COCO ₂ H	94	18,31
Ph	CN	97	33, 35
Ph	CO ₂ Et	40–80	10, 26, 27
Ph	COPh	41	10, 17, 26, 29, 36, 37, 368
Ph	H	—	35
Ph	Ph	—	28
Ph	CO ₂ Et	52	10
Ph	COCH ₂	—	33
Ph	NO ₂	36	56
4-O ₂ N-C ₆ H ₄	CONH ₂	89	35
4-O ₂ N-C ₆ H ₄	SO ₂ CH ₃	—	
4-Br-C ₆ H ₄	2-Quinolyl	79	46
2-Cl-C ₆ H ₄	CH ₂ CH ₂ OH	38	66
4-H ₃ C-C ₆ H ₄	Cl	40	50
2-H ₃ COC ₆ H ₄	SO ₂ Ph	—	11,23
Ph	CONHCO ₂ Et	—	41

oxadiazolone (30), resulting from diazonium displacement of the halogen (Eq.3). Table 2 illustrates the scope of the utility of active methylene compounds in the syntheses of formazans.

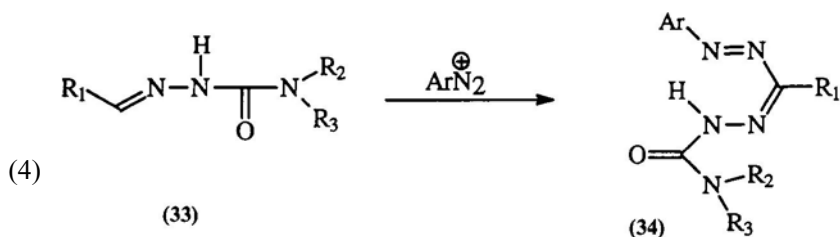


*Synthesis of 3-Cyano-1,5-diphenylformazan (32).*³⁵ A solution of 18.8g of aniline in 100ml of 6M hydrochloric acid was diazotized at



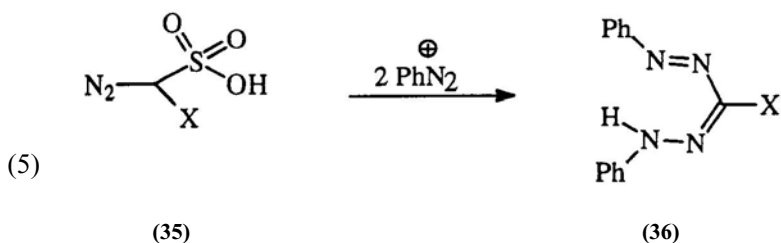
– 10 °C with a solution of 16 g of sodium nitrite in 40 ml of water. To this solution was added a solution of 8.5 g of cyanoacetic acid in 100 ml of water cooled to 0 °C. The resulting solution was neutralized with 200 ml of a 20% solution of sodium hydroxide when an intense red color formed. The formazan was precipitated with 10% hydrochloric acid, filtered, and air dried. The crude formazan was recrystallized from 400 ml of ethanol to yield 9.5 g (40%) of golden platelets mp 158 °C.

Aldehyde semicarbazones with two substituents on the terminal amino group (but not the hydrazino) (**33**) react with diazonium salts to yield N-carbamoyl-substituted formazans (**34**) (Eq. 4).^{47,48} A sulfonic acid deriva-

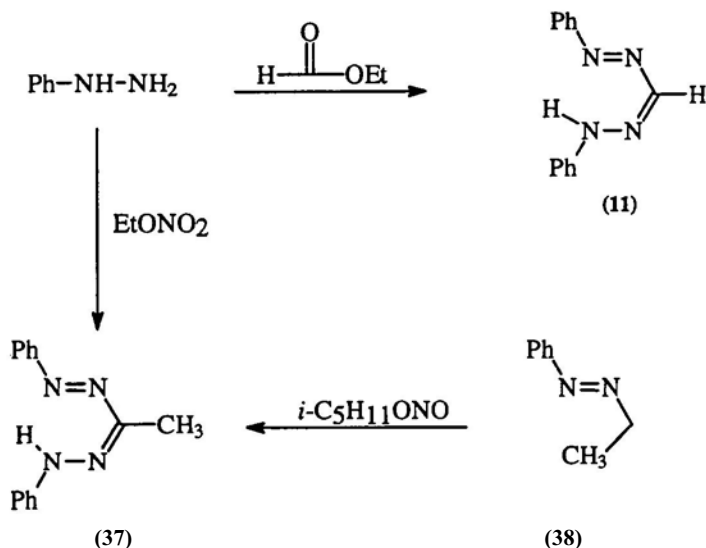


R₁, R₂, R₃ = Alkyl or Aryl

tive of ethyl diazoacetate (**35**) reacts with aryl diazonium salts in alkaline solution to yield an alkoxycarbonyl-substituted formazan (**36**) (Eq. 5).⁴⁹⁻⁵¹ Diazomethane disulfonic acid behaves similarly.



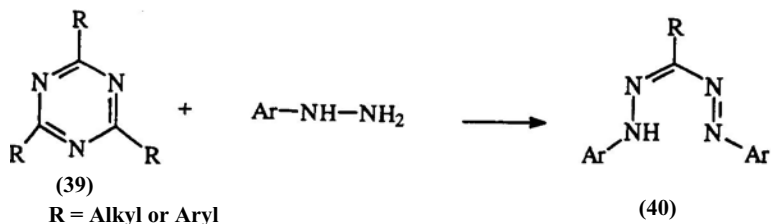
X = CO₂Et or SO₃H



Scheme 4

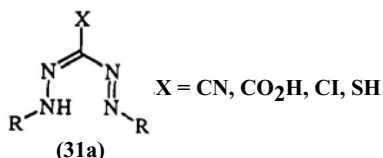
7.3.1.2. From Hydrazines

Ethyl formate^{34,52} or orthoformate^{53,54} reacts with two equivalents of phenylhydrazine to yield 1,5-diphenylformazan (**11**); the reaction takes place under acidic conditions and involves an oxidation. Under basic conditions, ethyl nitrate reacts at the methylene position to yield 3-methyl-1,5-diphenylformazan (**37**) which can also be obtained from the reaction of phenylazoethane (**38**) with isoamyl nitrite (Scheme 4).^{8,68} Aryl hydrazines react with a variety of s-triazines (**39**) to yield 1,5-diaryl formazans with hydrogen, methyl, or phenyl groups in the 3-position as in **40** (Eq. 6).⁵⁶ Hydrazines have also been reported to react with benzotrichloride^{55,658} and *sym*-diamino tetrazine⁶⁵⁹ to yield formazans.

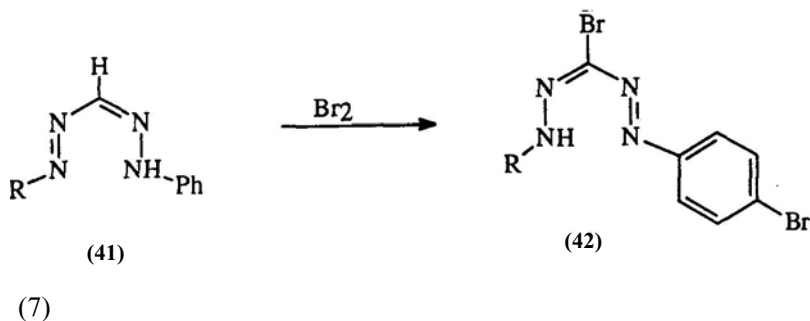


7.3.1.3. From Other Formazans

Formazans can undergo a variety of reactions leading to different formazans. These transformations include the reaction of substituents on the aromatic ring such as the hydrolysis of esters and nitriles,⁵⁷ the reduction of nitro groups to amines,⁵⁸ as well as esterification of carboxylic acids through their silver salts.⁵⁷ Replacement of *C*-nitro formazans³⁸ and *C*-halo formazans^{42, 43, 60-68} with amino, hydroxy, and mercapto groups as well as other halogens (**31a**) have been reported. The decarboxylation of *C*-carboxyl

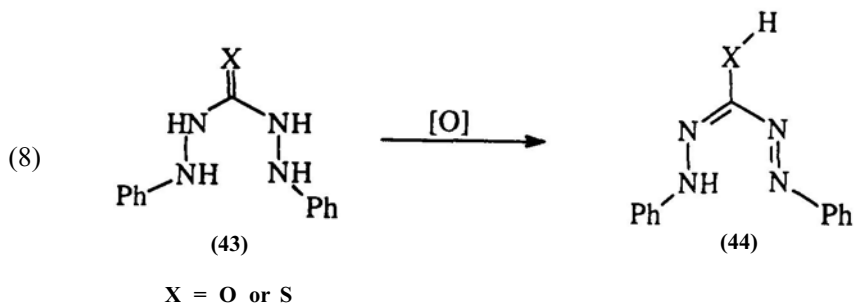


formazans has also been reported.^{57, 59} The reaction of formazans with bromine leads to the replacement of 3-hydrogen by bromine as well as ring bromination, **41** to **42** (Eq. 7).⁵¹

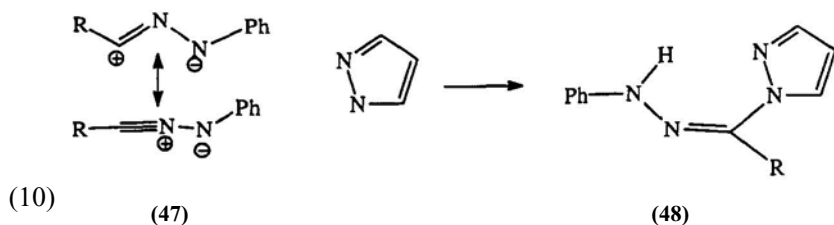
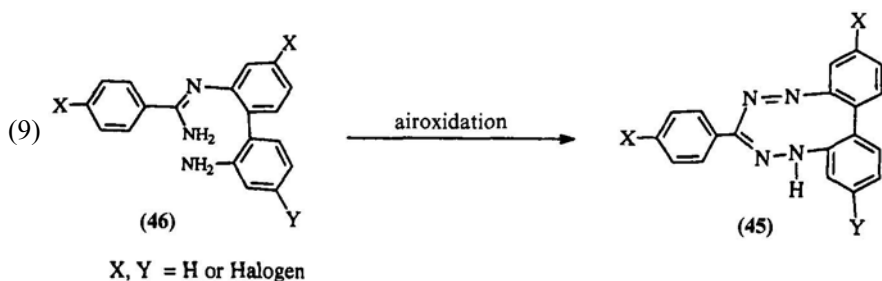


7.3.1.4. Miscellaneous Methods

Diaryl carbazides and thiocarbazides, e.g., **43**, can be oxidized at alkaline pH to yield *C*-hydroxy or *C*-mercapto formazans (**44**) (Eq. 8).^{68, 129} The replacement of *C*-halo formazans is considered to be a better method⁶⁰ for the preparation of **44**. A class of cyclic formazans (**45**) can be obtained by air oxidation of amidrazones (**46**) (Eq. 9).^{69, 73, 101, 102} Though this is formally a formazan, there are no reports of its oxidation reactions. In a



related reaction, nitrilimines, e.g., **47**, which can be conveniently generated by the action of lead tetraacetate on aldehyde hydrazones, react with pyrazole to form the aryl hydrazone of 1-acyl pyrazole (**48**), a structure akin to formazan (Eq. 10).^{71,72}

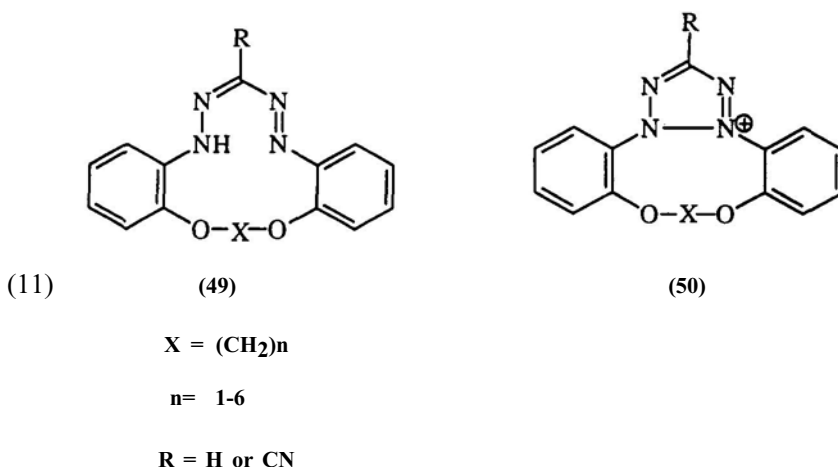


7.3.1.5. Oxidation of Formazans

A variety of oxidizing agents have been used to effect the transformation of formazans to tetrazolium salts. The choice of the reagent is still empirical and depends on the solubility properties of the formazan as well

as the resulting tetrazolium salt. The ease of oxidation is also influenced by the nature of the substituent.

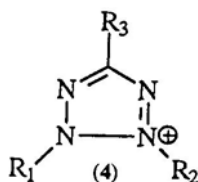
The earliest oxidations were effected with "nitrous fumes" and later with mercuric oxide and isoamyl nitrite.⁷⁴ Lead tetraacetate in acetic acid is in many cases the reagent of choice, but the removal of by-products can present some difficulties.⁷⁵ *N*-Haloimides and amides in alcoholic solutions have been reported to yield essentially pure tetrazolium salts⁷⁶ and have been found specially useful in the preparation of heteroaryl-substituted tetrazolium salt.^{77,78} The novel formazans **49** have been successfully oxidized to **50** using *N*-chloro succinimide (Eq. 11).⁷⁹ *tert*-Butyl hypo-



chlorite in chloroform or dioxane has also been reported to give good yields of tetrazolium Salts.⁸⁰ Chlorine⁸¹ and bromine⁸² have been reported to be effective oxidizing agents, although nuclear halogenation on aromatic rings can occur in some cases. Lead sesquioxide,⁸³ tribromophenol-bromine,⁸⁴ and ammonium peroxodisulfate⁸⁵ have also been reported. Hydrogen peroxide is generally ineffective, but can be very efficient in the presence of a catalyst such as ferrous ions or vanadium pentoxide.⁸⁷⁻⁹⁰ Recently, oxidations under phase transfer catalysis conditions have been studied and show great promise with potassium permanganate and nitrous acid.⁹¹⁻⁹³ Many formazans are air sensitive and in some cases aerobic oxidation can be used as a preparative method of tetrazolium salts.^{31,58,95}

Electrochemical oxidation has also been reported to result in good yields of tetrazolium salts.^{97,98} Treatment of formazans with boron trifluor-

Table 3. Synthesis of Tetrazoliums from Oxidation of Formazans



R ₁	R ₂	R ₃	Oxidizing agents ^a	Yields (%)	Refs.
Ph	Ph	H	A	85	70
Ph	Ph	CH ₃	B	81	74,260
Ph	Ph	OH	D	80	74,260
Ph	Ph	SH	E	20	56
Ph	Ph	CO ₂ H	D	80	74,260
Ph	Ph	Ph	A	58	70, 74,260
Ph	Ph	Ph	F	57	12
Ph	Ph	Ph	G	89	81
Ph	Ph	Ph	H	75	85
Ph	Ph	Ph	I	60	80
Ph	Ph	Ph	J	78	93
Ph	Ph	Ph	K	26	86
Ph	Ph	Ph	L	89	94
Ph	4-H ₃ CO-C ₆ H ₄	Ph	C	70	76
Ph	Ph	1,2-Ethylene	B	20	100
Ph	Ph	1,4-Phenylene	A	58	100
Ph	Ph	(CH ₂) ₆	F	24	117

^a A = Alkyl nitriteB = Pb(OAc)₄C = *N*-halomideD = N₂O₄

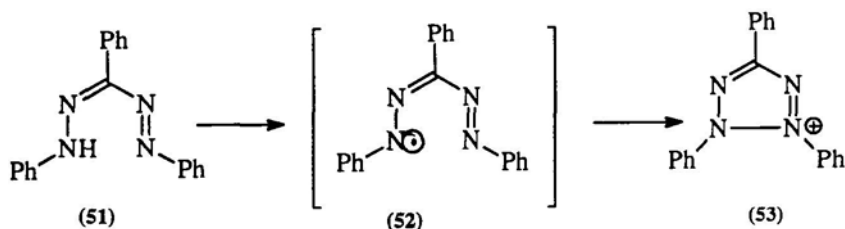
E = Air

F = HgO

G = Cl₂H = S₂O₈²⁻I = *t*-BuOClJ = MnO₄⁻/phase trans.K = BF₃Et₂OL = SO₂Cl₂

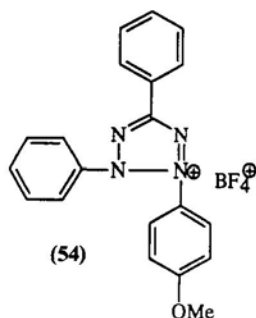
ide etherate⁸⁶ or thionyl chloride⁹⁴ has also been reported to yield tetrazoliums. Photooxidation has been suggested as a preparative method.⁹⁶ This will be discussed in Section 7.5.2.5. Table 3 illustrates the use of various oxidizing agents in the synthesis of tetrazoliums.

Wedekind and Stauwe⁹⁹ studied the oxidation of 3-substituted formazans and concluded that ease of oxidation depended on the steric effects of the 3-substituent. More recently, Hegoraty *et al.*¹⁰⁰ studied the reaction of formazans with bromine. It proceeds via an odd-electron species such as **52** favoring an electronic substituent effect (Scheme 5). The rate of reaction increases with electron-donating substituents. Similar conclusions have been reached using thalium(III) as the oxidant.^{101,102}



Scheme 5

*Synthesis of 2-(4-Methoxyphenyl)-3,5-diphenyltetrazolium tetrafluoroborate (54).*⁷⁶ To a stirred solution of 7.0 g of 1-(4-methoxyphenyl)-3,5-



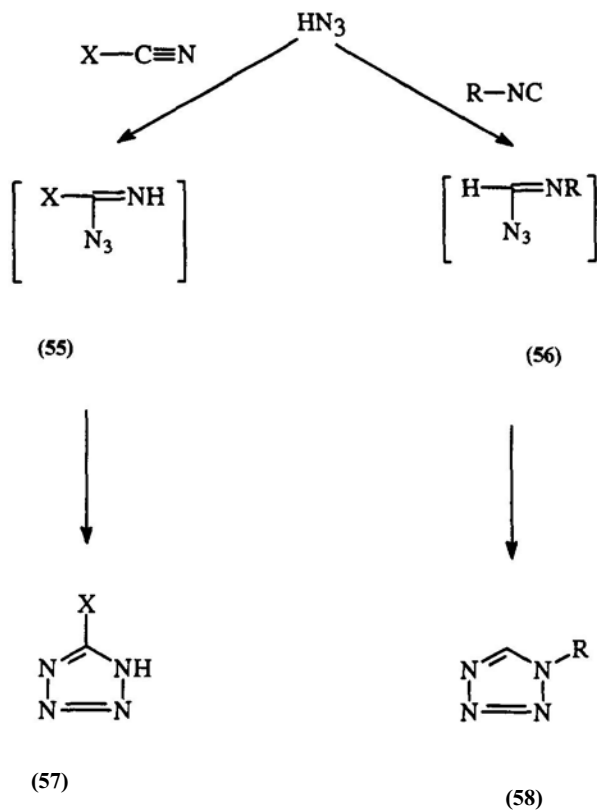
diphenylformazan in 400 ml of ethyl acetate was added a solution of 8.0 g of *N*-bromosuccinimide in 200 ml of ethyl acetate. The solution became colorless followed by partial precipitation. The yellow oily mass solidified on decantation of the solvent. It was taken up in 1500 ml boiling water, cooled, and filtered. The tetrazolium salt was precipitated by the addition of 200 ml 2 M sodium tetrafluoroborate. The off-white crystals were recrystallized from acetonitrile/ether, filtered, and air dried to yield 6.1 g (70%) of the tetrazolium salt.

7.3.2. From Tetrazoles

Extensive reviews of synthetic methods and properties of tetrazoles have been published.^{103,651 - 653}

7.3.2.1. From Hydrazoic Acid

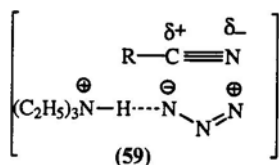
The addition of hydrazoic acid to carbon—nitrogen unsaturated bonds as in hydrogen cyanide, nitriles, and isonitriles leads to unsubstituted, 5-, or



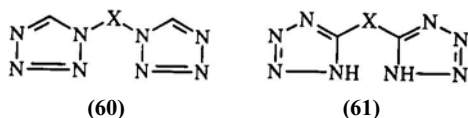
X	Yield(%)	Ref	R	Yield(%)	Ref
H	80	105	C ₆ H ₅	16	124
<i>i</i> -C ₃ H ₇	87	104	<i>n</i> -C ₆ H ₁₃	57	125,126
O-C ₆ H ₄	93	106,120	(C ₂ H ₅) ₂ N-C ₂ H ₄	69	121
SCH ₃	71	107, 116,118			
N(CH ₃)-C ₆ H ₄	20	113			
N(<i>n</i> -C ₄ H ₉) ₂	85	114			
4-H ₂ N-C ₆ H ₄	10	114			
C ₆ H ₅	76	106			
4-O ₂ N-C ₆ H ₄	97	106			
NH ₂	quant	105,115			
CO ₂ C ₂ H ₅	--	114			

Scheme 6

1-substituted tetrazoles **57** or **58**, respectively, through the unstable imide-azide intermediates **55** and **56** (Scheme 6).^{104,105} In some special cases, a 1,3-dipolar addition (**59**) is proposed.^{32,472} The reaction is usually conduc-

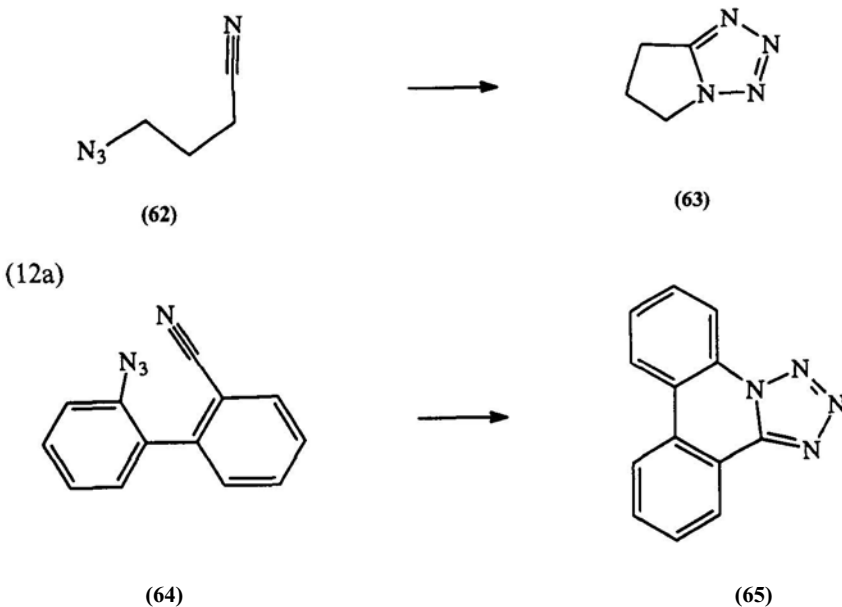


ted in a sealed tube and is very slow. The use of ammonium azide in dimethylformamide not only avoids the use of the hazardous hydrazoic acid but also accelerates the reaction.^{106,107,654} Tributyltin azide and trimethylsilylazide in combination with trimethyl aluminum have been reported as safe sources of hydrazoic acid.¹⁰⁸⁻¹¹¹ Substituted nitriles such as cyanofornates, cyanamides, cyanates, and thiocyanates lead to 5-alkoxycarbonyl and alkyl or arylamino, 5-alkyl or aryl ethers, and thioether derivatives, respectively.^{106,109,112-114} 5-Amino tetrazole has been prepared from dicyandiamide which acts as a source of cyanamide.¹¹⁵ It is assumed that the cyanamides react as the tautomeric carbodiimides. Using bisisonitriles or dinitriles, this reaction leads to nitrogen- or carbon-linked ditetrazoles **60** and **61**, respectively.^{106,124,125} The intramolecular addition of organic azido

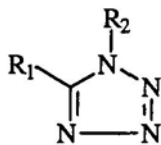
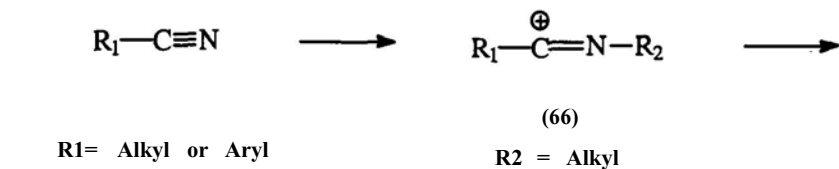


nitriles, e.g., **62** and **64**, can lead to 1,5-fused ring tetrazoles, e.g., **63** and **65** (Eq. 12a,b).¹¹⁶ Though many bistetrazoles and fused ring tetrazoles are important therapeutic agents, there are no reports of their conversion to the corresponding tetrazolium salts.

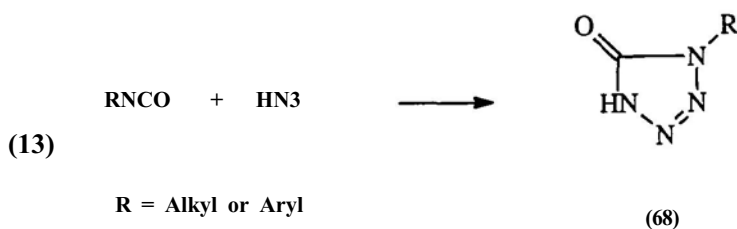
Nitrilium salts, e.g., **66**, prepared from the alkylation of nitriles, react with sodium azide to yield 1,5-disubstituted tetrazoles, e.g., **67** (Scheme 7).¹²¹ The Schmidt reaction,¹²² a versatile method for the preparation of 1,5-disubstituted tetrazoles from ketones and hydrazoic acid, can now be regarded as a special case of azide addition to nitrilium salts.¹²³



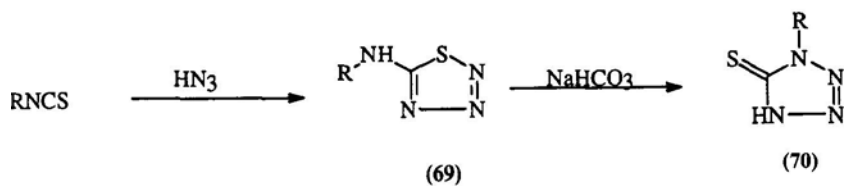
Isocyanates¹³² react with appropriate azide salts to yield 1-substituted tetrazoline-5-ones **(68)** (Eq. 13). By contrast, isothiocyanates^{133,134} react with hydrazoic acid to yield the aminothiatetrazole **(69)** which rearranges to the thione **(70)** under mild alkaline conditions (Scheme 8). Ugi and co-worker^{126,127} found that when the reaction of isonitriles and hydrazoic



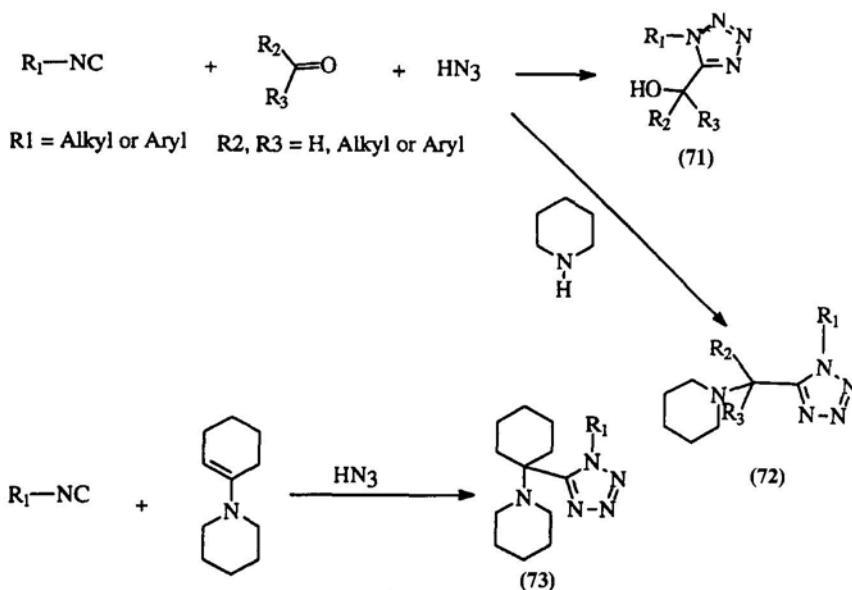
(67)
Scheme 7



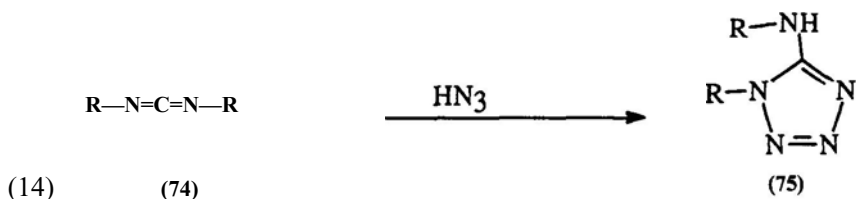
acid is carried out in the presence of an aldehyde or ketone, 1,5-disubstituted tetrazoles (**71**) are obtained. A similar reaction occurs when acyl hydrazones or azines are used in place of the ketone or aldehyde.¹²⁷ The addition of a secondary amine¹²⁸ to the reaction mixture, or the direct reaction with an enamine in place of the ketone or aldehyde,¹²⁸ leads to amino-substituted



Scheme 8

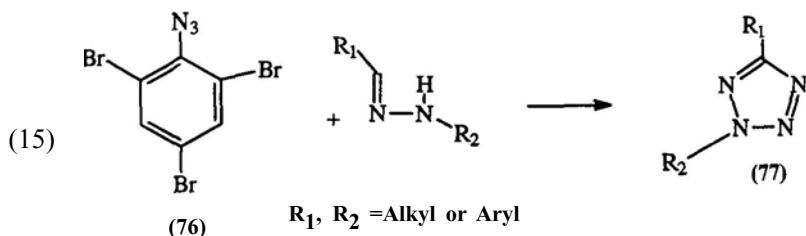


Scheme 9

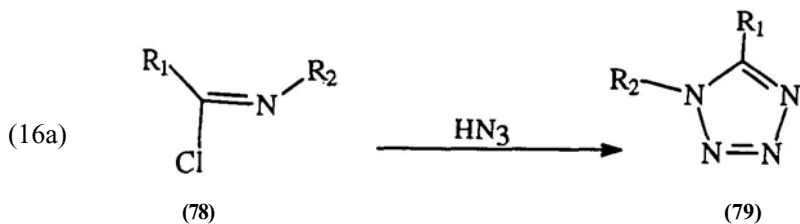


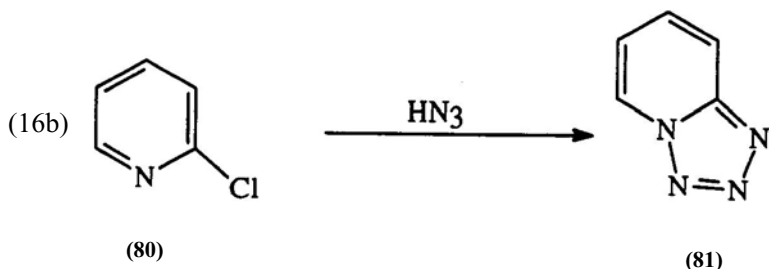
R = Alkyl or Aryl

tetrazoles, e.g., **72** and **73**, in near-quantitative yields (Scheme 9).^{128 - 131} 1,5-Disubstituted tetrazoles with a nitrogen substituent in the 5-position (**75**) can be obtained from the reaction of carbodiimides (**74**) and hydrazoic acid (Eq. 14).^{135 - 138} Aryl azides, particularly hindered ones, e.g., **76**, react with aldehyde hydrazones to yield 2,5-disubstituted tetrazoles (**77**) in moderate (25—75%) yields (Eq. 15).^{39, 139, 140}

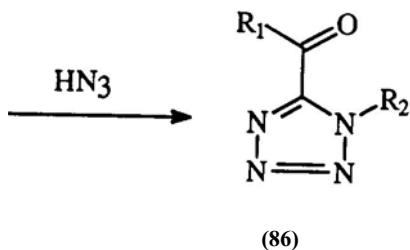
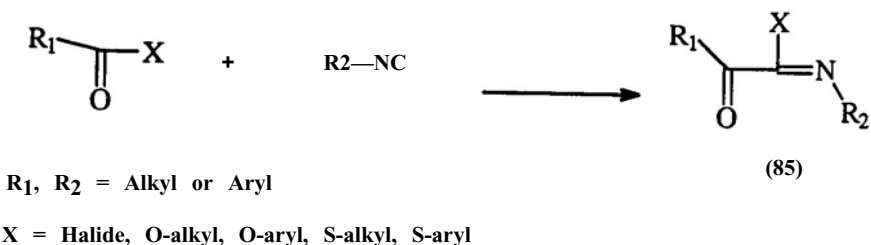


Besides addition reactions, azides or hydrazoic acid can also yield tetrazoles through displacement reactions. Thus, halide displacement in imide chloride (**78**) yields 1,5-disubstituted tetrazoles (**79**), and in 2-chloropyridine (**80**), yields tetrazolopyridine (**81**) (Eq. 16a,b).^{141 - 143} Vinylogous





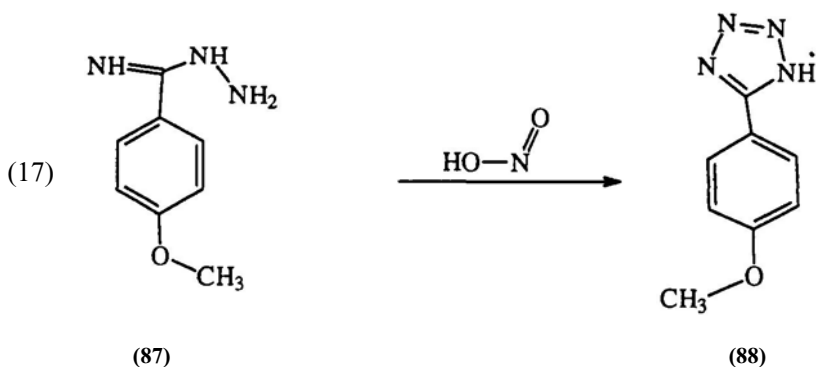
imide chlorides, e.g., **82** react with excess azide to give fair yield (32—70%) of the 5-dimethylamino vinyl derivative (**84**) through a series of displacements and rearrangements as shown in Scheme 10.^{144–146} Traces of the 1-dimethylamino isomer arising from a vinyl migration, are also isolated. C-acylimide halides (**85**), which are readily generated from the reaction of acyl halides and isonitriles, yield 1-substituted 5-acyl tetrazoles (**86**).¹⁴⁷ Such displacements are not restricted to halides but can be extended to alkoxy, aryloxy, alkyl, and arylthio groups (Scheme 11).^{148,149} Recently, the reduction of alkylated tetrazolopyridines has received some attention (see Section 7.3.3.2).



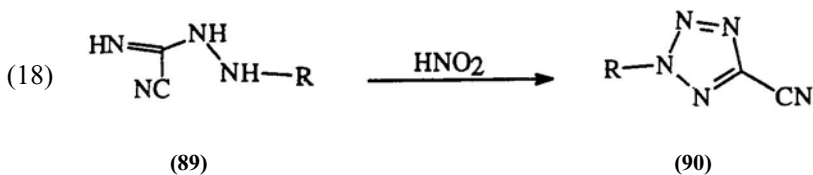
Scheme 11

7.3.2.2. From Nitrous Acid

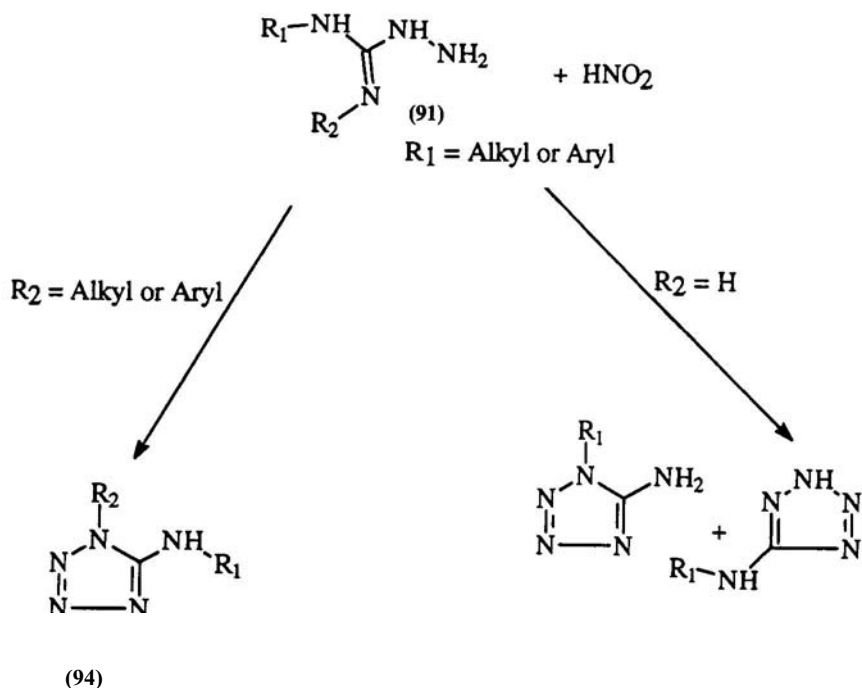
Nitrous acid or alkyl nitrites react with a number of nitrogen compounds to yield tetrazoles. For example, hydrazidines (**87**), which can be prepared *in situ* from the corresponding iminoesters, react with nitrous acid or its derivatives to give 1-substituted tetrazoles (**88**).¹⁵⁰⁻¹⁵² This reaction (Eq. 17), is one of the most extensively used methods for the synthesis of



many substituted tetrazoles. It is worth noting here that the first reported synthesis of an amino tetrazole involved the diazotization of aminoguanidine.¹⁵³ Diazotization of 1-cyanoformimidic acid hydrazide (**89**) yields 5-cyanotetrazole (**90**).¹⁵⁴ The diazotization of the phenyl derivative [(**89**) $\text{R} = \text{Ph}$], obtained from the reaction of cyanogen and phenylhydrazine, was in fact the basis of the first recognized synthesis of a tetrazole ring (Eq. 18).^{155,156} 1-Alkyl-2-aminoguanidine (**91**) ($\text{R}^2 = \text{H}$) is diazotized to two isomeric tetrazoles **92** and **93** in which the 5-amino-1-alkyl isomer (**92**) predominates.¹¹⁷ However, disubstituted aminoguanidines ($\text{R}_2 = \text{alkyl}$



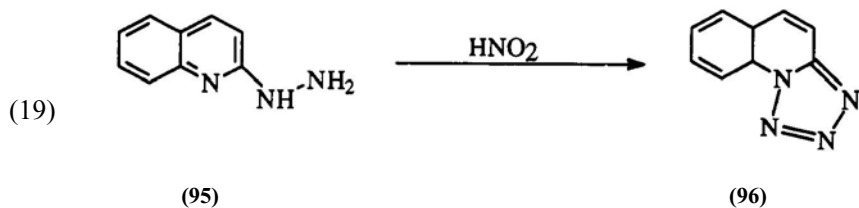
$\text{R} = \text{H, Alkyl or Aryl}$

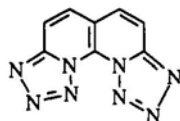


Scheme 12

or aryl) yield the corresponding 5-aminotetrazoles **(94)** only (Scheme 12).^{157, 158}

Fused ring tetrazoles such as **96** are obtained from the reaction of nitrous acid with heterocyclic hydrazines **(95)** (Eq. 19).^{159, 160} This method is also suitable for the preparation of fused ring ditetrazoles such as **97**.^{161 - 165}



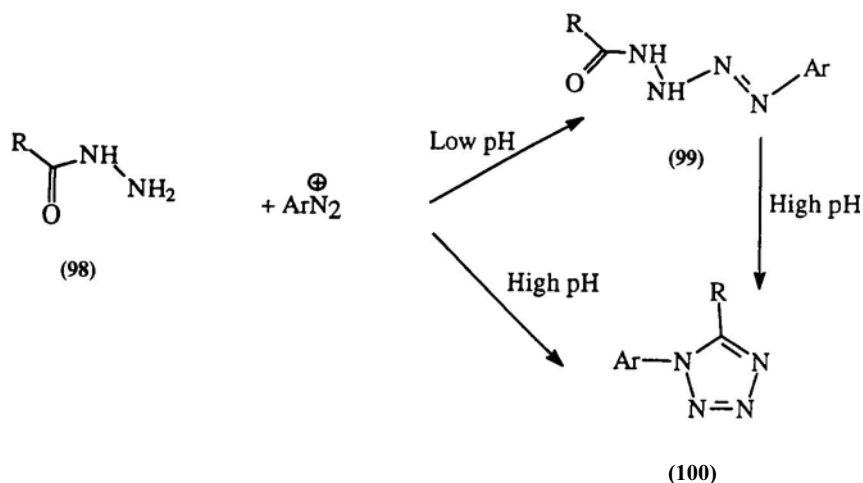


(97)

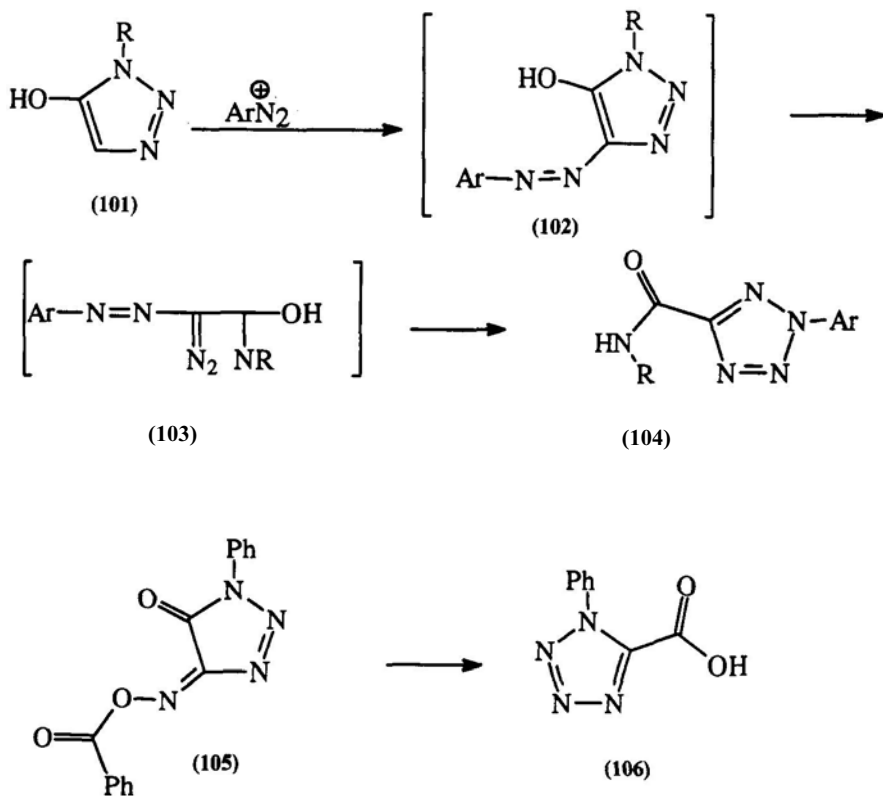
7.3.2.3. From Diazonium Salts

1,5-Disubstituted tetrazoles are conveniently prepared from acyl hydrazines (**98**) and diazonium salts.¹⁶⁶ The reaction proceeds through the intermediate tetrazenes (**99**) followed by cyclization to the tetrazole (**100**) (Scheme 13). The intermediate can be isolated under mildly basic conditions. Symmetrically 1,2-diacylated hydrazines yield 1-substituted tetrazoles through the elimination of one of the acyl groups.¹⁶⁶⁻¹⁶⁸ Diformylhydrazine is a very convenient starting material for 1-substituted tetrazoles.¹⁶⁶ Unsymmetrically 1,2-diacylated hydrazine usually results in mixtures.¹⁶⁹

Diazonium salts couple to hydroxy-substituted vicinal triazoles (**101**) with subsequent rearrangement of the hydroxy arylazo compounds (**102**) to the carbamoyl tetrazole (**104**).¹⁷⁰ An open-chain intermediate (**103**) has been proposed.¹⁶⁹ This rearrangement is similar to that of the benzoyl



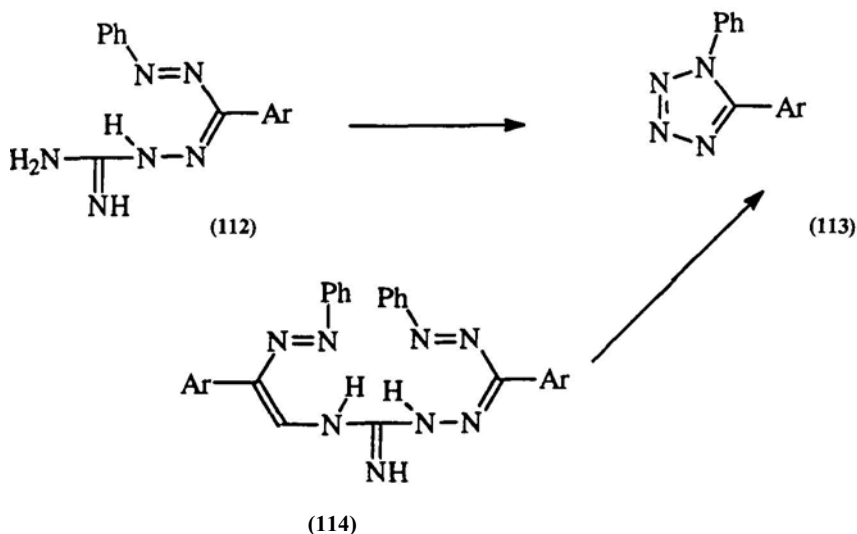
Scheme 13



Scheme 14

derivative of isonitroso triazolinone (**105**) to the tetrazole (**106**) (Scheme 14).^{171 - 174} 3-Amino isoxazoles also rearrange to tetrazoles through a triazine intermediate.^{173,174}

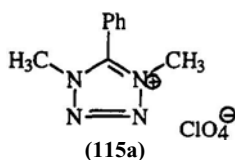
Diazonium salts react with bis(methylsulfonyl) methane (**107**) ($\text{X} = \text{SO}_2\text{CH}_3$) to yield a 1,3-diaryl tetrazolinone (**111**). The reaction proceeds through an azo (**108**) and a tetrazene (**109**) intermediate, followed by hydrolysis under the alkaline conditions of the reaction to the carbonyl compound (**110**). An unexplained oxidation leads to the 1,3-diaryl tetrazolinone (**111**) either directly or through the intermediate **110a** (Scheme 15).^{18,35} A similar reaction occurs between a diazonium salt and the potassium salt of phenyl hydrazonomethane disulfonic acid (Scheme 15).¹⁷⁵



Scheme 16

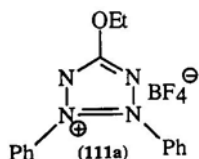
expected 4-position, whereas at higher temperatures, the thermodynamically more stable 2,4-dialkyl 5-aryl isomer is obtained, possibly through the isomerization of the 1,4-dialkyl derivative.^{178-180,473} In the alkylation of 1-aryl-5-methyl tetrazole, the ratio of 3,5- and 4,5-dialkyl isomers changes with the nature of the alkylating agent.¹⁸¹ In contrast, in the alkylation of 1,5-dialkyl tetrazoles, the 1,3,5- to 1,4,5-isomer ratio is either closer to 1:1 or exclusively the 1,4,5-trialkyl isomer.¹⁸² 1-Alkyl tetrazoles also undergo alkylation at the 4-position.¹⁸³ 2,5-Disubstituted tetrazoles are less reactive than the 1,5 isomers, but yield 1,3,5 isomers exclusively,^{180,183-187} whereas 1-aryl-5-(dialkylaminovinyl) tetrazoles (**84**) undergo alkylation at the 4-position exclusively.¹⁸² The alkylation of mesoionic tetrazoles takes place on the exocyclic heteroatom in good yields.¹⁸⁸

*Synthesis of 1,4-Dimethyl-5-phenyltetrazolium perchlorate (115a).*¹⁸⁰ 1.92 g of 1-methyl-5-phenyltetrazole was added with stirring to 2.06 g of



dimethyl sulfate. The mixture was heated for 15 h at 35 °C, cooled, and poured into 20 ml of ether and stirred. The ether layer was removed by decantation and the residue was washed with ether (4 × 20 ml), hexane (2 × 20 ml), and benzene (2 × 20 ml). The resulting solid was taken up in 10 ml of water and 1 ml of 57% perchloric acid was added. The product was filtered, washed with cold water, and recrystallized from isopropanol to yield 2.1 g of the tetrazolium salt (67%), mp 159—160°C.

*Synthesis of 5-Ethoxy-1,3-diphenyltetrazolium tetrafluoroborate (111a).*¹⁸⁸
1.2 g of 1,3-diphenyltetrazolium-5-olate was added to a solution of 1.0 g



of triethyloxonium tetrafluoroborate in 20 ml of dichloromethane. After 16 h, ether was added and the precipitate collected. Recrystallization from acetone/light petroleum (bp 40—60 °C) gave 1.6 g of product (9%) mp 174°C.

7.3.3. Direct Methods

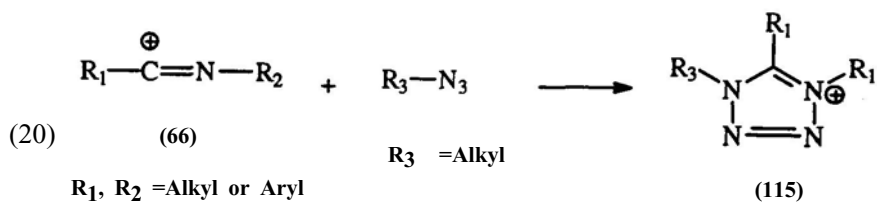
Some of the methods used for the preparation of either formazans or tetrazoles can lead directly to tetrazolium salts when appropriate substituents are present.

7.3.3.1. From Nitrilium Salts

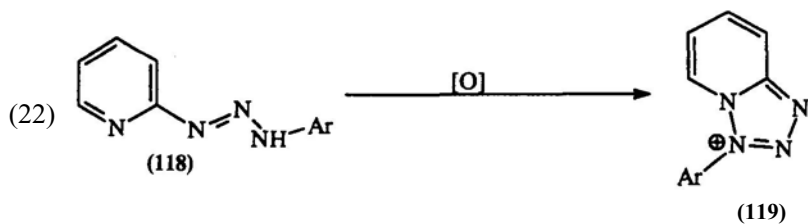
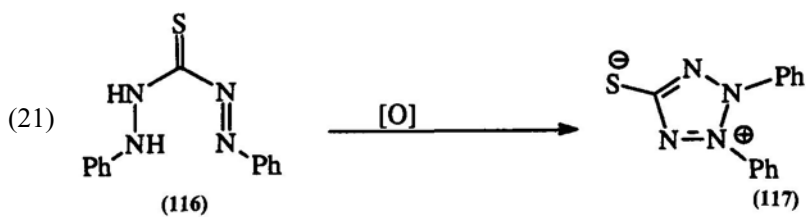
Nitrilium salts (**66**) react with alkyl or aryl azides to give good yields of 1,4,5-trisubstituted tetrazolium salts (**115**) (Eq. 20).^{189,255}

7.3.3.2. Oxidations

Ferricyanide oxidation of 1,5-disubstituted thiocarbazones (**116**) give the mesoionic tetrazolium salts (**117**) under mild conditions (Eq. 21).¹⁹⁰ This is in contrast to the strongly alkaline oxidation of carbazides leading to mercapto formazans as shown in Eq. 8 (Section 7.3.1.4). The heterocyclic triazine (**118**), obtained by the action of a diazonium salt on 2-

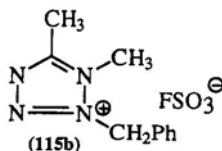


R_1	R_2	R_3	Yield (%)
CH_3	CH_3	CH_3	80
CH_3	CH_3	CH_2Ph	71
CH_3	C_2H_5	C_2H_5	58
Cyclohexyl	CH_3	CH_2Ph	60
<i>t</i> - D_4H_9	CH_3	CH_2Ph	60
Ph	CH_3	CH_3	75
Ph	CH_3	CH_2Ph	70
Ph	C_2H_5	C_2H_5	55
Ph	Ph	CH_3	78
Ph	Ph	CH_2Ph	65
Ph	Ph	Ph	52



aminopyridine, is oxidized by the action of tribromophenol-bromine in ethyl acetate at room temperature to the fused tetrazolium salt (**119**) in excellent yield (78—92%) (Eq. 22).¹⁹¹

*Synthesis of 2-Benzyl-1,5-dimethyltetrazoliumfluorosulfonate (**115b**).*¹⁸⁹
An equimolar mixture of acetonitrile and methyl fluoro-sulfonate was kept



at room temperature for 5 h. The resulting solid was washed several times with anhydrous ether and filtered. The product (75% yield), mp 123—124 °C, was used without further purification.

To the above product, dissolved in acetonitrile, was added an equimolar amount of benzyl azide and the solution stirred under reflux for 12 h. On cooling, the precipitated product was collected, washed with ether, and dried to yield 71% of the pure product.

*Synthesis of 3-Phenyltetrazolopyridinium bromide (**119**).*⁶⁶⁰ To a solution of 2.88 g of 1-(2-pyridyl)-3-phenyltriazine was added 4.92 g of 2,4,4,6-tetrabromocyclohexa-diene-1-one. The product precipitated within minutes and was isolated by filtration in 87% yield mp 278—280 °C.

7.3.4. From Other Tetrazolium Salts

As will be discussed later (Sections 7.4.2.1 and 7.4.2.2), tetrazolium salts are not stable under basic conditions. Depending on the substituent, however, acidic conditions may allow some transformations. Thus, 2,3,5-triphenyltetrazolium chloride can be converted to the disulfonic acid derivative by the action of concentrated sulfuric acid or oleum.¹

7.4. PROPERTIES OF TETRAZOLIUM SALTS

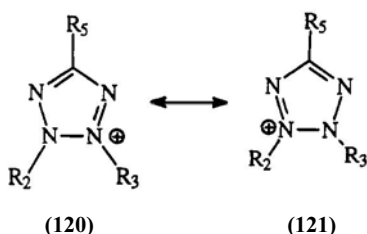
7.4.1. Physical Properties

Depending on the substituent, and to a lesser extent on the counterion, tetrazolium salts are generally crystalline colorless, or yellowish to orange solids. Although their solubility depends on the substituent pattern and the counterion, they are generally slightly soluble in water. Thus, tetrazolium

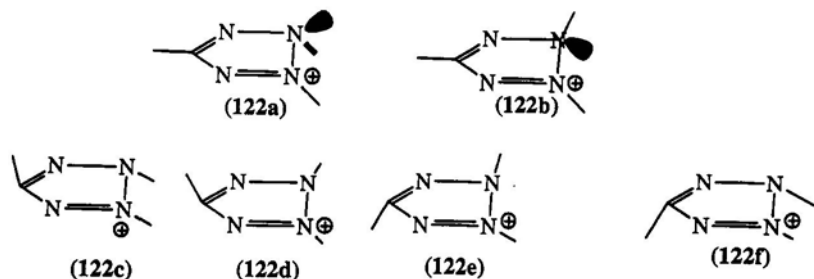
salts containing trimethylammonium groups on the aromatic substituents are very water soluble.¹ Sulfonates and phosphonates are highly water soluble.¹⁹² They are thermally stable up to 215 °C. Some toxic properties have been described.^{12,13,16,194–196}

7.4.1.1. Electronic Structure

Nineham¹ proposed that tetrazolium salts exist as resonance hybrids forms **(120)** and **(121)** (shown for 2,3-substituted ones). However, UV-



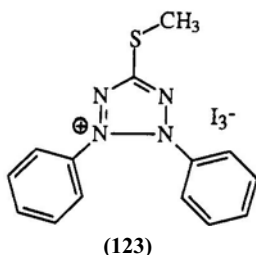
visible, IR, NMR, and differential calorimetric studies on unsymmetrically substituted 2,3,5-triaryl tetrazolium salts (with a substituted phenyl in the 5-position) indicate the existence of distinct isomers.^{197–206} Inversion at the trisubstituted nitrogen may be slowed down by the bulky aryl substituents on the adjacent nitrogen and the carbon, thus allowing conformational isomerism to occur, **122a** and **122b**.² Schiele and co-workers proposed the possibility of four stereoisomers **122c** to **122f** for tetrazoliums with different substituents at N2 and N3^{200,203} but the exact mechanism of the isomerization is not clear, and has received little or no attention since first reported. Contrary to the resonance model, molecular orbital calculations using CNDO approximations show unequal electron densities on the nitrogens.^{207,208} It is not clear that this nonequivalence, in addition to the



unequal twist of the substituents on the 2- and 3-positions (Section 7.4.1.2), can account for the isomerism.

7.4.1.2. Crystal Structure

X-ray structure analysis of 2,3-diphenyl-5-thiomethyltetrazolium triiodide (**123**) shows that the phenyl rings at the 2- and 3-positions are out of



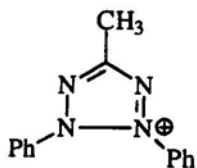
the plane of the tetrazolium ring by 69 and 58°, respectively. The bond distances in the tetrazolium ring are not equal. In contrast, 2,3-diphenyl-5-mercaptide shows extensive bond delocalization.^{209,210}

7.4.1.3. Mass Spectra

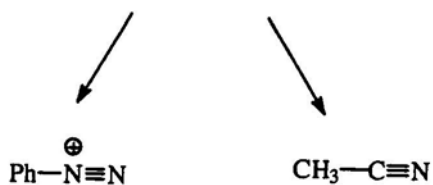
The fragmentation of tetrazolium salts under electron impact seems to follow characteristic paths. 5-Methyl-2,3-diphenyl tetrazolium (**124**) shows, in addition to the parent ion peak, peaks corresponding to the phenyl diazonium fragment and the complementary ion at m/z 132. At higher ionization energies, a strong peak at m/z 91 corresponding to the elimination of acetonitrile from the parent ion is observed (Scheme 17).²¹¹ By contrast, the mass spectrum of 1,4,5-trisubstituted tetrazoliums, e.g., **125** shows strong peaks corresponding to the nitrilium ions **126** and **127** as shown in Scheme 18).²¹² The mass spectrum of mesoionic tetrazoliums shows only 10% of the intact parent ion peak and mostly peaks corresponding to diazonium ions.²¹³ With thermospray mass spectrometric techniques, bistetrazolium salts form intact cations as a base peak.²¹⁴

7.4.1.4. NMR Spectra

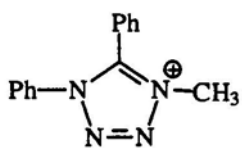
NMR spectroscopy is commonly used for the identification of isomeric tetrazolium salts. There are significant differences in the chemical shifts of C-methyl and N-methyl protons as shown in Table 4 for compounds **128**



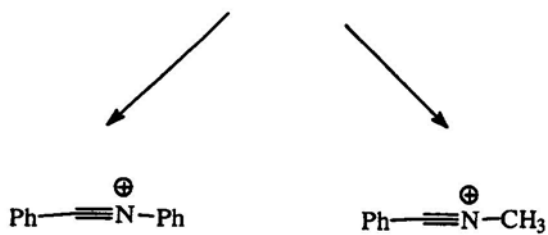
(124)



Scheme 17



(125)



(126)

(127)

Scheme 18

Table 4. ^1H -NMR Chemical Shifts (δ) of Methyl-Substituted Tetrazoliums **128** and **129**

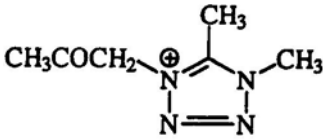
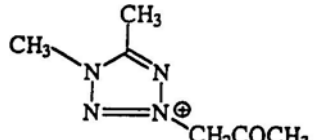
 (128)  (129)			
Compound	CH_2	N-CH_3	C-CH_3
128	6.00	4.44	2.92
129	6.12	4.37	2.86

Table 5. ^1H -NMR Chemical Shifts (δ) of Methyl-Substituted Tetrazoliums **130–135**

Compound	1- CH_3	3- CH_3	4- CH_3	5- CH_3
130	4.31	4.58	—	—
131	4.33	—	4.60	—
132	—	—	4.35	—
133	—	—	4.72	—
134	—	—	4.30	2.90
135	—	4.62	—	2.78

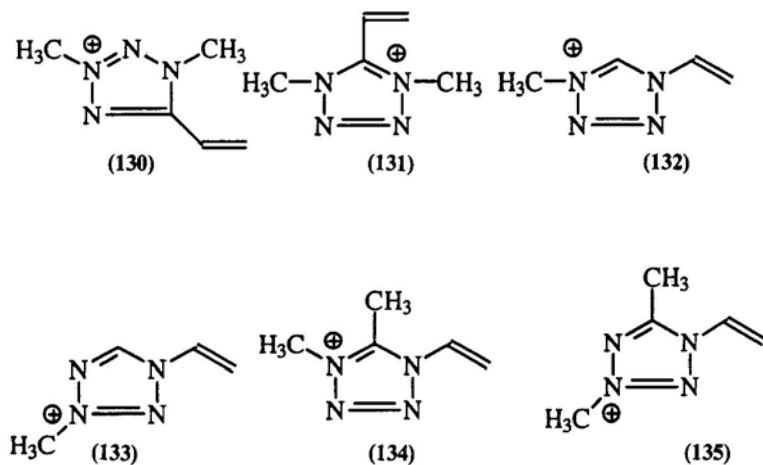


Table 6. ^1H -NMR Chemical Shifts (δ) of Trisubstituted Tetrazoliums **136** and **137**

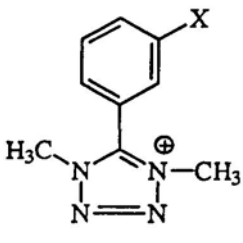
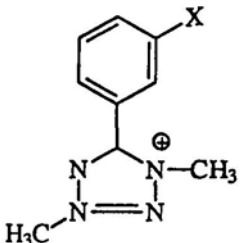
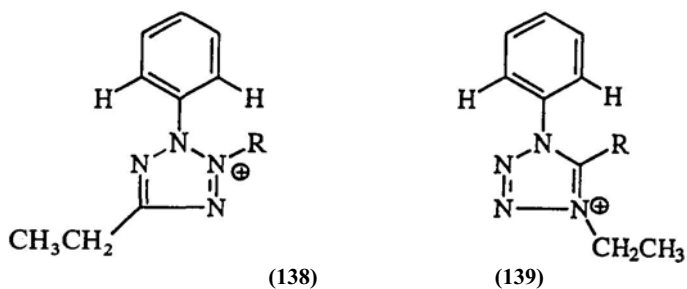
 (136)  (137)				
Compound	X	1-CH ₃	3-CH ₃	4-CH ₃
136	H	4.40	—	4.40
136	NO ₂	4.45	—	4.45
137	H	4.60	4.80	—
137	NO ₂	4.65	4.90	—

Table 7. ^1H -NMR Chemical Shifts (δ) of *N*-Phenyl Tetrazoliums **138** and **139**



Compound	R	H(R)	CH ₃	CH ₂	H(Ph-2'/6')
138	H	11.30	1.80	4.96	8.02
138	CH ₃	2.93	1.73	4.73	7.75
138	CH ₂ Cl	5.31	1.76	4.88	7.78
139	H	2.93	1.82	5.07	8.26
139	CH ₂ Cl	5.45	1.80	5.03	8.24

Table 8. ^1H -NMR Chemical Shifts (δ) of Disubstituted Tetrazoliums **140** and **141**

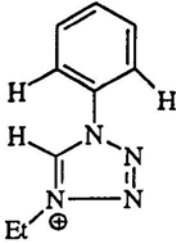
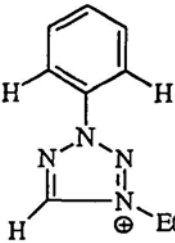
 (140)  (141)			
Compound	H-5	Ph-2'-H	Ph-3'/14'-H
140	10.74	7.81	7.56
141	10.26	8.26	7.81

Table 9. ^{13}C -NMR Chemical Shifts (δ) of Methyl-Substituted Tetrazoliums **130–135**

Compound	1-CH ₃	3-CH ₃	4-CH ₃	5-CH ₃	Ring
130	37.80	38.80	—	—	162.7
131	38.80	—	37.75	—	162.7
132	—	—	38.33	—	142.1
133	—	44.18	—	—	149.3
134	—	—	37.04	8.96	152.6
135	—	44.10	—	9.93	159.1

Table 10. ^{15}N -NMR Chemical Shifts (δ) of Methyl-Substituted Tetrazoliums **130–132**

Compound	N1	N2	N3	N4
130	-71.5	-101.2	-17.5	-148.7
131	-148.1	-17.9	-101.2	-76.1
132	-127.5	-22.2	-14.4	-142.5

and **129**,¹⁸⁷ Table 5 for **130—135**,²¹⁹ and in Table 6 for **136** and **137**.^{180,215} The 5-ring proton chemical shifts in 5-unsubstituted tetrazolium as well as the *ortho* proton in phenyl substituents at the 5-position are sensitive to *N*-substituents and substitution patterns as shown in Table 7 for **138** and **139** and in Table 8 for **140** and **141**.^{181,218}

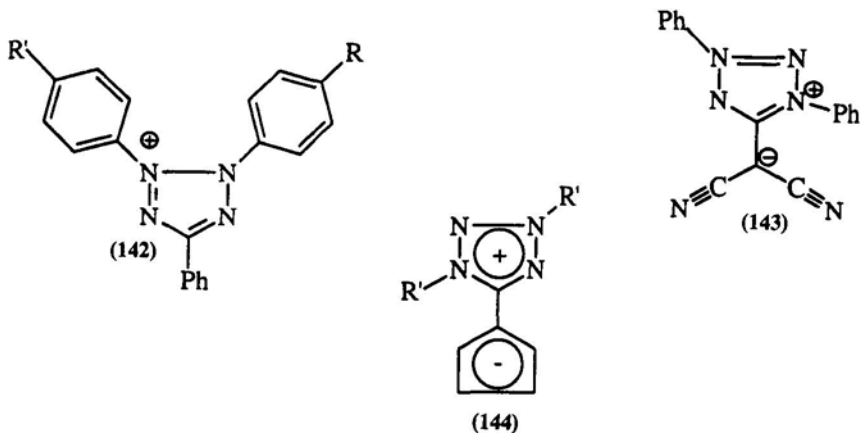
Carbon-13 NMR has been used in the study of thiolate and disubstituted tetrazolium derivatives.^{217–219} The chemical shifts of both the substituent and ring carbons show strong sensitivity to substituents as shown in Table 9 for **130—135**.²¹⁹ Tetrazolium salts have also been studied by nitrogen-15 NMR (Table 10).^{220,221}

7.4.1.5. IR Spectra

IR spectroscopy has been utilized to demonstrate the existence of isomers for 2,3,5-triaryl-substituted tetrazolium salts.²⁰³ In a systematic study, Arnold and Schiele list and assign all of the vibrational frequencies of 33 triaryl tetrazolium perchlorates.²²¹ Of particular interest are the ring frequencies. Only one of the carbon—nitrogen frequencies is dependent on substitution. For example, C=N1 in triaryl tetrazoliums shifts from 1530cm⁻¹ in the triphenyl derivative to 1527cm⁻¹ in the 5-(4-chlorophenyl), to 1523cm⁻¹ in the 2-(4-chlorophenyl), and to 1544cm⁻¹ in the 5-(4-methoxyphenyl) derivatives. By contrast, the C=N4 frequency, ranging between 1146 and 1149 cm⁻¹, is insensitive to substitution for the mesoionic thiolate series.²²² The assignment is refined by using nitrogen-15 in positions 1 and 4 of the tetrazolium ring.²²³

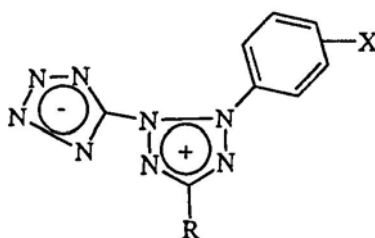
7.4.1.6. UV/Visible Spectra

There have been very few systematic studies of the electronic spectra of tetrazolium salts. Generally, they have strong UV absorption maxima



at 240—280nm.²²⁴ The introduction of electron-donating substituents on the phenyl group at the 2-position leads to a red-shift which extends further on the introduction of an electron-withdrawing substituent in the phenyl group at the 3-position. For example, in **142**, $R' = N(CH_3)_2$, the absorption maximum shifts from 440 nm when R is H to 475 nm when R is NO_2 .^{82,225} In mesoionic tetrazoliums, e.g., **117**, the major absorption band appears at 326—333nm.²²⁵ In more conjugated systems such as the dicyanomethylene (**143**) or the heptafulvalene analogue (**144**), this band appears at 396 nm in acetonitrile.²²⁶ In an interesting extension of this phenomenon, Shchipanov²²⁸ prepared a series of mesoionic bis tetrazolium betaines (**145**). The effect of substituents on the major absorption band is summarized in Table 11.

Table 11. UV/Visible Spectra of Tetrazolium Ylide (**145**)



(145)

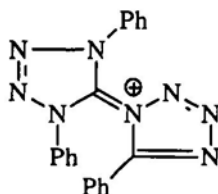
R	X	λ (nm)
CH ₃	H	275
C ₃ H ₇	H	281
C ₆ H ₅	H	245
Styryl	H	290
3-NO ₂ -C ₆ H ₄	H	235
4-NO ₂ -C ₆ H ₄	H	277
2-HO-C ₆ H ₄	H	247, 305
3,4-(OCH ₃) ₂ C ₆ H ₃	H	225, 215, 296
4-(CH ₃ N) ₂ C ₆ H ₄	H	227, 332, 422
3-CH ₃ O-4-HOC ₆ H ₃	H	225, 275, 300
4-NO ₂ -C ₆ H ₄	4-N(CH ₃) ₂	275, 470
3-NO ₂ -C ₆ H ₄	4-N(CH ₃) ₂	230, 257, 475
4-N(CH ₃) ₂ -C ₆ H ₄	4-N(CH ₃) ₂	265, 327, 450
2-HOC ₆ H ₄	4-N(CH ₃) ₂	255, 300, 452
CH ₃	4-N(CH ₃) ₂	265, 450
Ph	3-NHCOCH ₃	250
Ph	3-NH ₂	255, 400
Ph	4-N(CH ₃) ₂	245, 460

The spectra of these highly conjugated betaines are solvent sensitive. The absorption maximum of **144** is 450 nm in carbon tetrachloride and 392nm in dimethylsulfoxide. The spectra of a number of substituted diaryl thiobetaines correlated well with Kossower's Z solvent polarity indicators.²²⁷

7.4.2. Chemical Properties

7.4.2.1. Action of Acids

In general, tetrazolium salts are stable in mineral acids. This stability has allowed a number of synthetic transformations such as ester and amide hydrolysis and demethylation of ethers etc.²⁰⁹⁻²¹² This is not the case with tetrazolium salts containing a heterocyclic substituent in the 3-position. They tend to decompose in mineral acid to the corresponding tetrazoles.²³⁰ Tetrazolyl-substituted tetrazoliums (**146**) and mesoionic tetrazoles, e.g., **145**, are unaffected by acids.^{228,232}

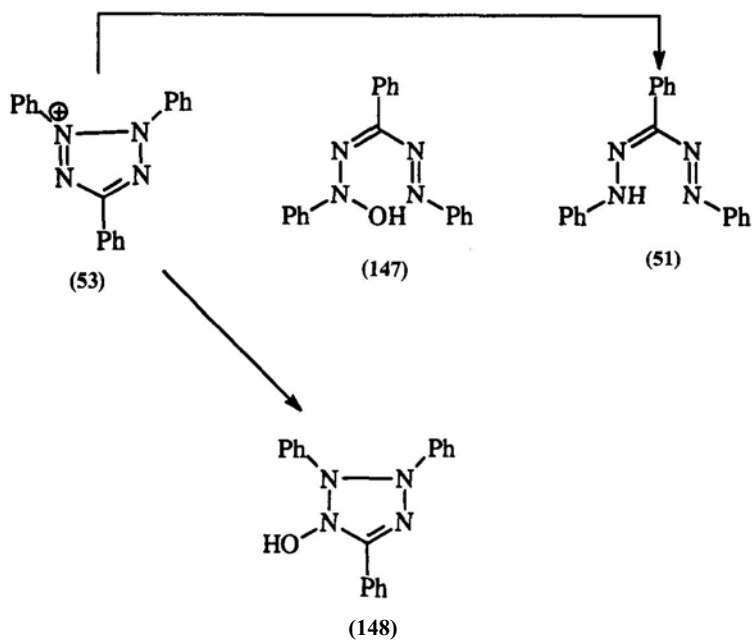


(146)

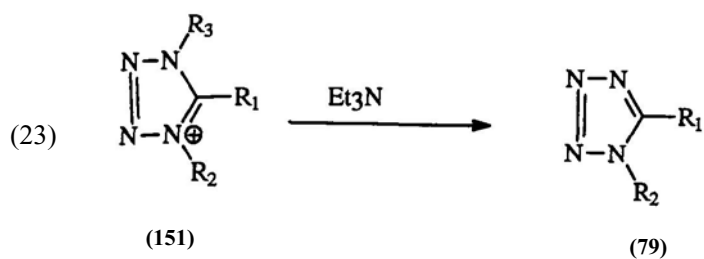
7.4.2.2. Action of Bases

Tetrazolium salts are unstable in basic solutions yielding intense colors. This reaction is still little understood.^{233,234} In the reaction of 2,3,5-triphenyltetrazolium with hydroxide, it is postulated that a hydroxide ion is involved first as a counterion later leading to the hypothetical *N*-hydroxyformazan (**147**).²²⁹ Weiner studied the kinetics of this reaction and identified 1,3,5-triphenylformazan in 10% yield. In concentrated alkaline solutions, the *N*-hydroxytetrazole (**148**) has been isolated from triphenyltetrazolium chloride (Scheme 19).^{235,236}

The reaction of 1,4-disubstituted tetrazoliums (**149**) with aliphatic tertiary amines such as triethylamine leads via deprotonation to **150** followed by ring opening to form a carbodiimide (**74**) with the loss of nitrogen (Scheme 20).^{237,238} Under the same conditions, 1,4,5-trisubstituted

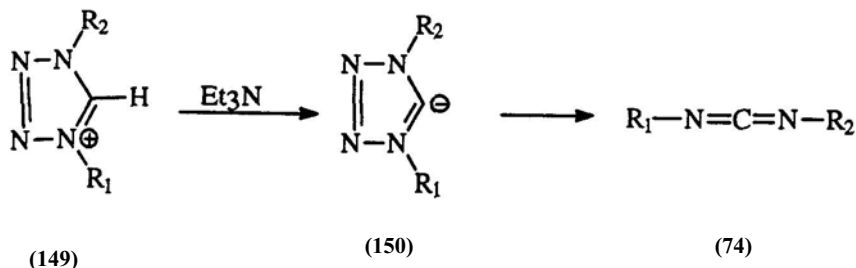


Scheme 19



R_1, R_2 = Alkyl or Aryl

R_3 = Alkyl



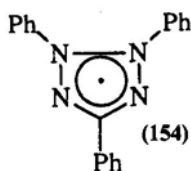
R_1, R_2 = Alkyl or Aryl

Scheme 20

tetrazoliums (**151**), on the other hand, undergo dealkylation yielding 1,5-di-substituted tetrazoles (**79**) (Eq. 23).²³⁹

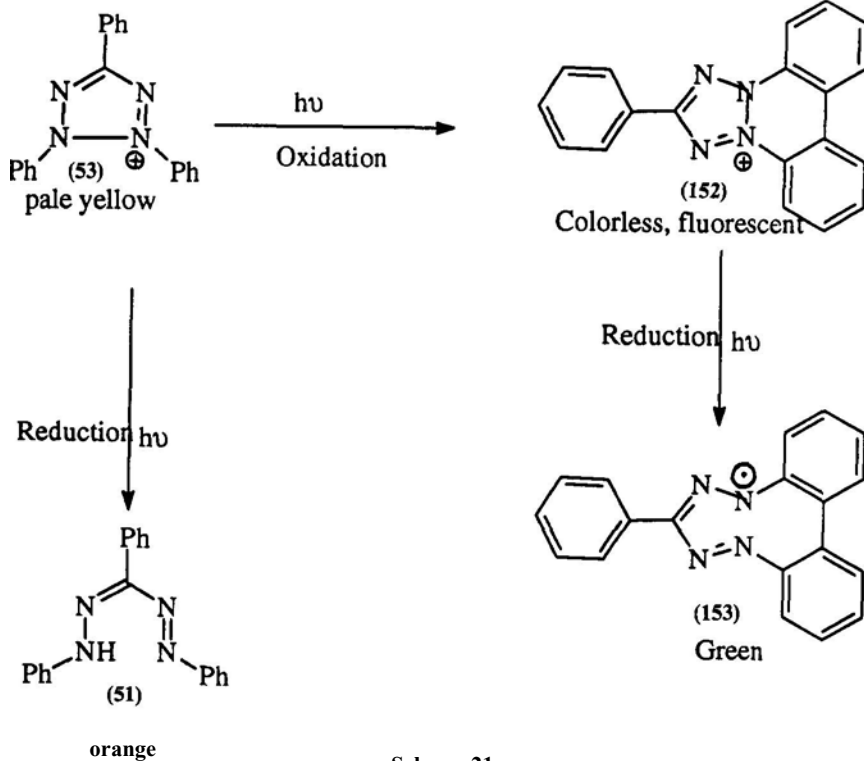
7.4.2.3. Action of Light

Solutions of tetrazolium salts, e.g., **53**, have been reported to both become colored and bleached under the influence of both UV and visible light. Several workers have attributed this phenomenon to photoreduction to the corresponding formazan (**51**) and the formation of a fluorescent colorless compound (**152**) through photooxidation.²⁴⁰⁻²⁴³ The reduction of **152** under UV or blue light to the intense green radical structure (**153**) has also been reported (Scheme 21).²⁴⁴ A one-electron reduction product (**154**) is proposed as a short-lived intermediate in the photoreduction.²⁴⁵



This reaction is influenced by solvent. Thus, in aqueous solutions 2,3,5-triphenyltetrazolium chloride yields 1,3,5-triphenylformazan (**51**), while in ethanol **152** is obtained. The mechanism of this reaction is not well understood.²⁴⁶⁻²⁵⁴

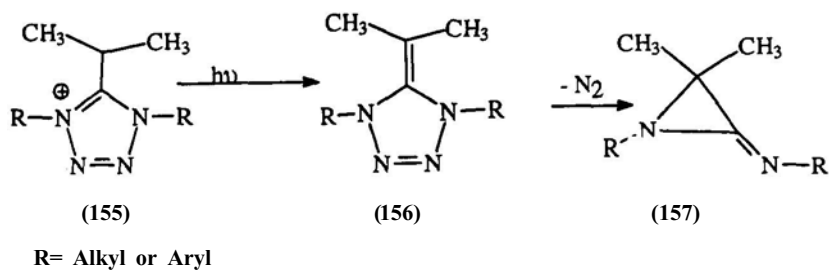
In a related manner, gamma radiolysis of tetrazolium salts also yields formazans.^{256,257} Pulse radiolysis in aqueous solutions leads to tetrazole



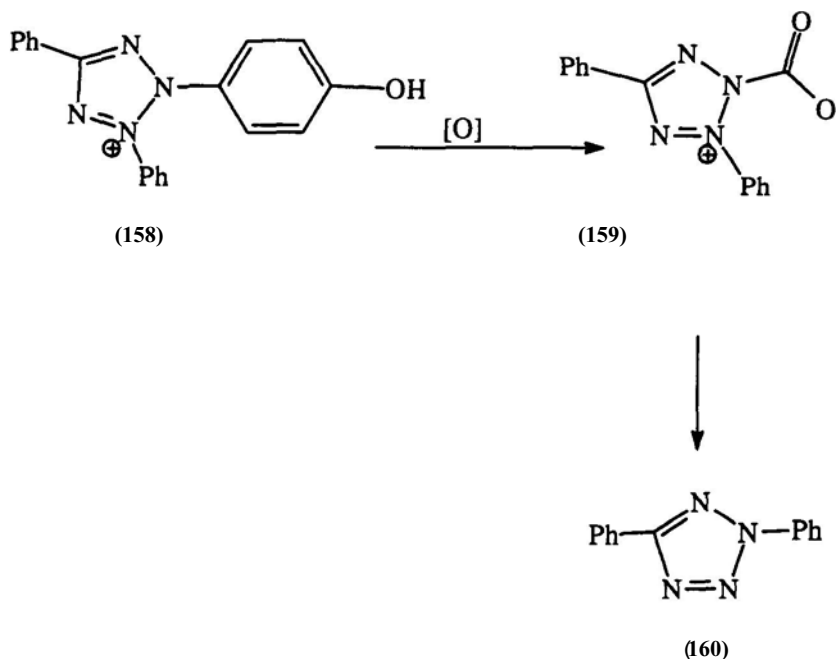
Scheme 21

radicals which can then disproportionate to formazan anions and tetrazoliumsalts.²⁵⁸⁻²⁶⁰

Unlike others, the 5-isopropyl tetrazoliums (**155**) undergo photodeprotonation to **156** which then yields the aziridine (**157**) with the elimination of nitrogen (Scheme 22).²⁵⁴



Scheme 22



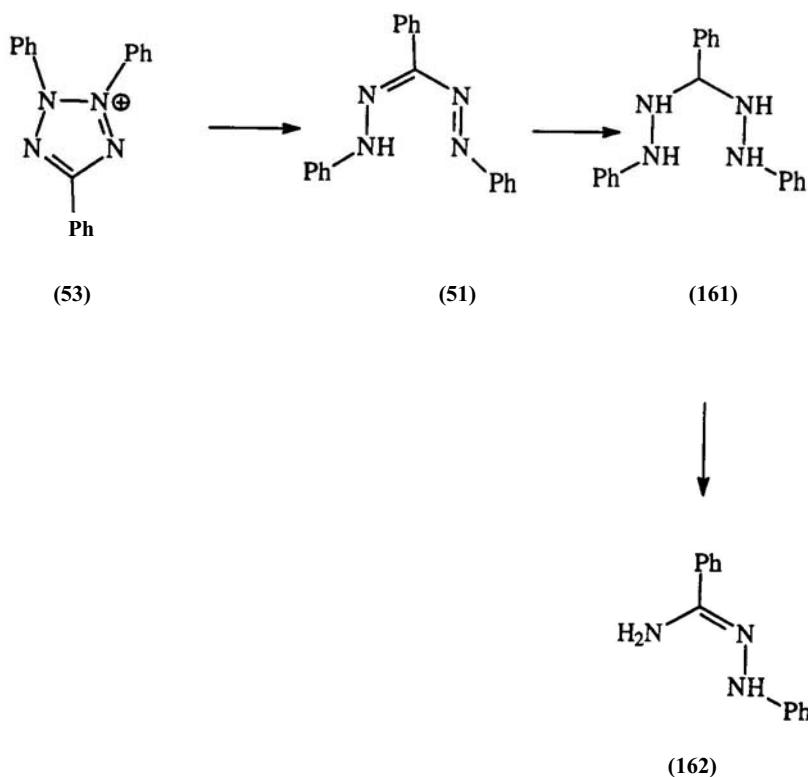
Scheme 23

7.4.2.4. Action of Oxidizing Agents

Tetrazolium salts are resistant to oxidation, but substituents on the ring can undergo oxidation. For example, 2-(4-hydroxyphenyl) tetrazolium (**158**) reacts with permanganate to give the tetrazole **160** via **159** (Scheme 23).^{205,208,211}

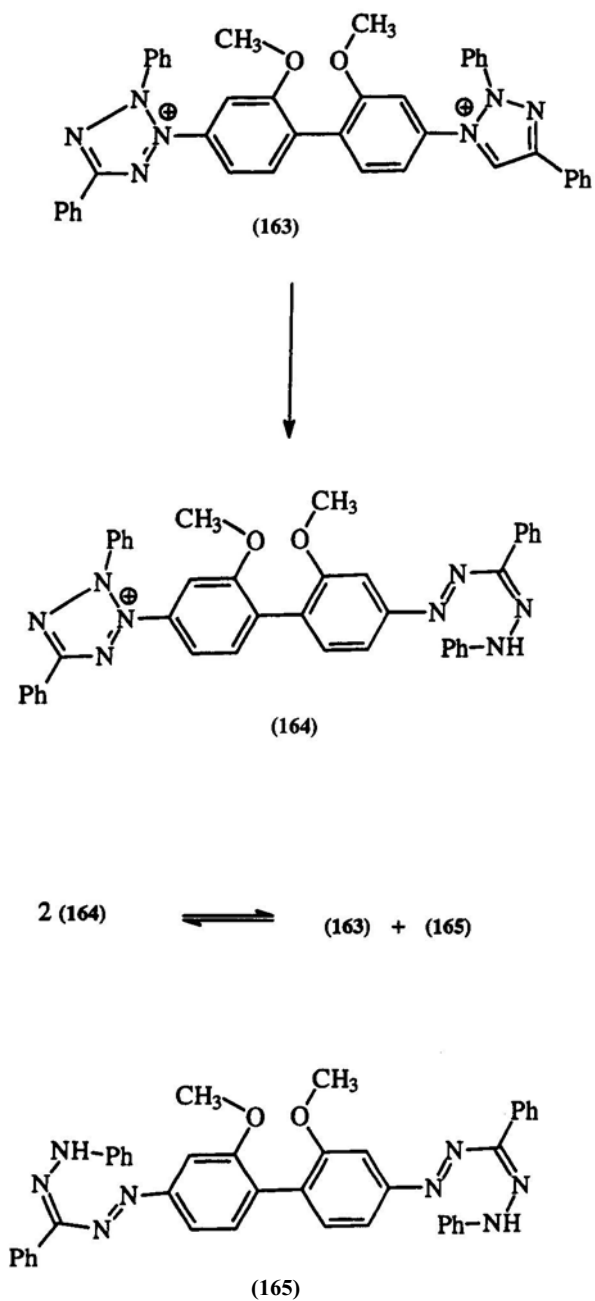
7.4.2.5. Action of Reducing Agents

This is by far the most important reaction of tetrazolium salts and accounts for the bulk of their many applications. A large variety of reagents can reduce tetrazolium salts, e.g., **53** to formazans, e.g., **51**. Ascorbic acid, hydrazine, and hydroxylamine have been recommended for the preparation of formazans from tetrazolium salts.²⁴⁵ Stronger reducing agents such as ammonium sulfide, sodium amalgam, sodium dithionite, and catalytic hydrogenation can further reduce the formazans to the amidrazones, e.g.,

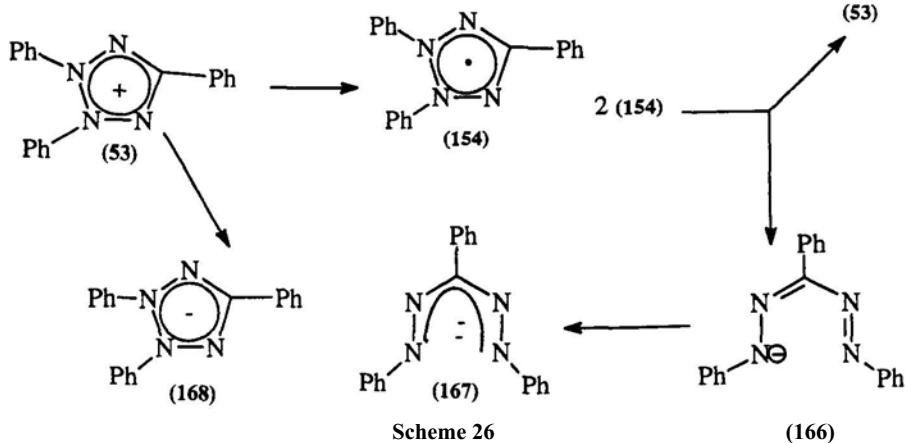


Scheme 24

162, through the hydrazidine intermediate (**161**) (Scheme 24).^{76,196} In symmetrically substituted tetrazoliums, as in **53**, the amidrazones can be isolated. However, unsymmetrically substituted tetrazoliums lead to complex mixtures. It is claimed that irrespective of the reducing agent, the reduction proceeds cleanly to the formazan whenever the formazan can be precipitated during the reduction.²⁴⁴ As in photochemical reduction, the free radical intermediate (**154**) is proposed as the first step in the reduction as confirmed for many systems by ESR spectroscopy.^{226,261–264} The reduction of the commercially important bis tetrazolium salt (**163**) gives a red mono formazan (**164**) which then disproportionates to the blue formazan (**165**) and the bis tetrazolium salt (**163**) (Scheme 25).^{267–271} The reduction of mono and bis tetrazolium salts by reduced nicotinamide adenine dinucleotide, NADH, is very important in biochemistry and will be discussed in Section 7.6.2.



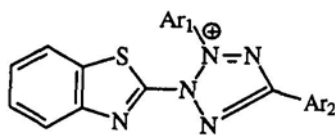
Scheme 25



7.4.2.6. Electrochemical Reduction

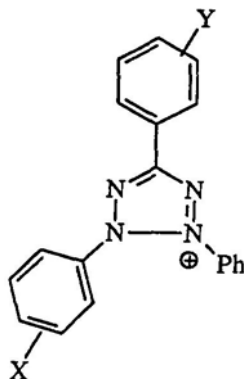
Electrochemical methods have been used extensively to elucidate the mechanism of reduction of tetrazolium salts. In aprotic media, the first step is a reversible one-electron reduction to the radical **154** as confirmed by ESR spectroscopy.^{256,266} As shown in Scheme 26, this radical can then disproportionate to the tetrazolium salt and the formazan anion (**166**) or take up another electron to the formazan dianion (**167**). The formation of the dianion through a direct reduction or through the intermediate tetrazolyl anion (**168**) has also been proposed.^{272-281,294} In aqueous solutions, where protonation/deprotonation equilibria contribute to the complexity of the reduction process, the reduction potentials are pH dependent and a one-electron wave is seldom observed.

The reduction potentials, measured by scanning voltammetry, are substitution dependent.²⁸² As shown in Table 12 for a series of triaryl tetrazoliums (**169**), the reduction becomes easier when electron-withdrawing substituents are present. This is in agreement with the polarographic data on a series of benzothiazolyl tetrazolium salts (**170**).²⁸³ With bis tetrazolium



(170)

Table 12. Reduction Potentials
of Tetrazolium Salt (**169**)



(**169**)

X	Y	$E(\text{mV})^a$
H	H	-294
4-Cl	H	-269
4-CH ₃	H	-301
4-OCH ₃	H	-316
H	4-Cl	-249
H	3-Cl	-221
H	4-Br	-233
H	4-F	-256
H	4-CH ₃	-300
4-Cl	4-Cl	-222
4-Cl	4-CH ₃	-287
4-Cl	4-OCH ₃	-293
4-CH ₃	4-Cl	-236
4-CH ₃	4-CH ₃	-313
4-CH ₃	4-OCH ₃	-311
4-OCH ₃	4-Cl	-261
4-OCH ₃	4-CH ₃	-325

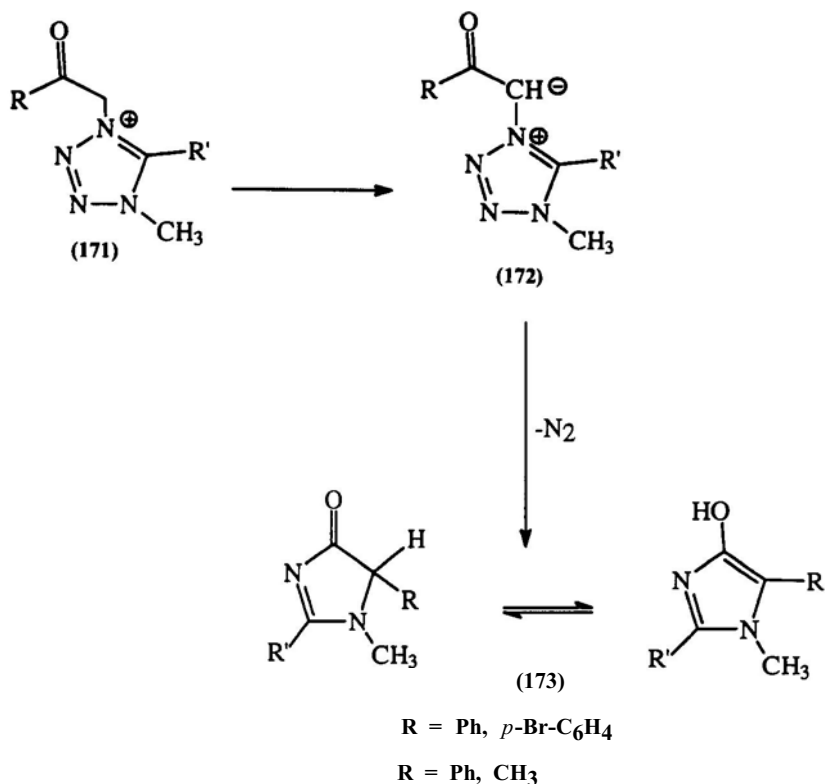
^aVersus Ag/AgCl.

salts in nonaqueous aprotic solvents, a series of one-electron steps have been identified leading to both the “monoformazans” and the “diformazans” **164** and **165** in Scheme 25.²⁸⁵ In aqueous and micellar media, two two-electron steps and one four-electron step have also been observed.^{284–288}

7.4.2.7. Miscellaneous Reactions

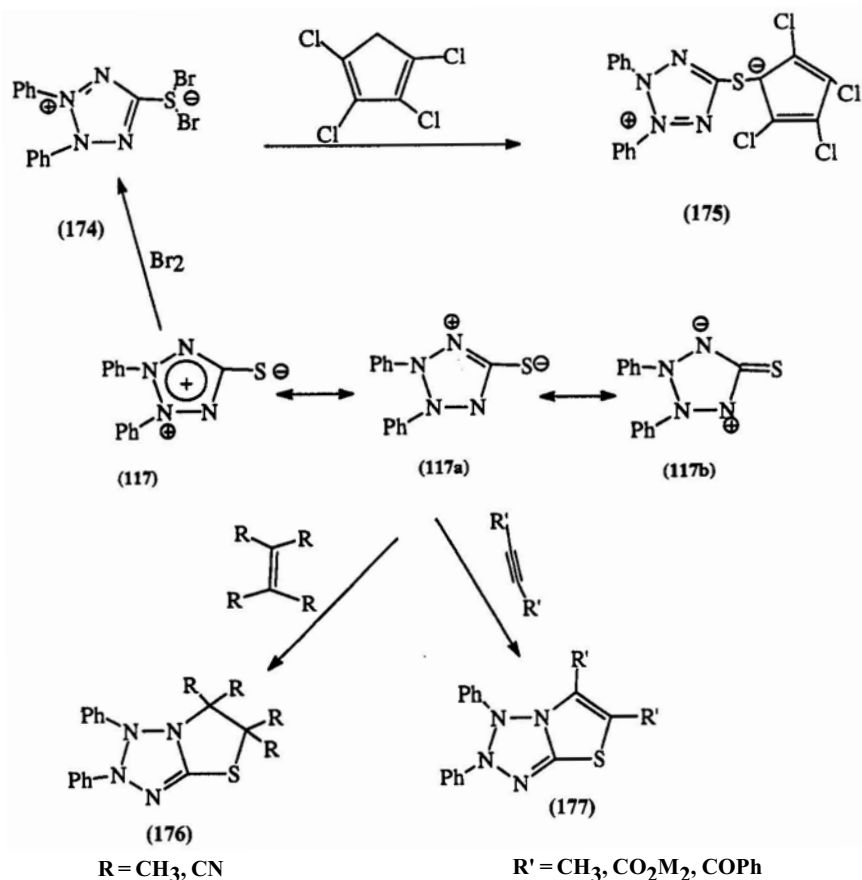
The methyl hydrogens in 1,3,5- and 1,4,5-trimethyl tetrazoliums, as well as the proton on C-5 in 2,3-disubstituted tetrazoliums are acidic, and can be abstracted with butyl lithium.^{289,290} Tetrazolium methylides, e.g., the dicyano derivative (**143**), and the phenacyl compound (**171**, R = Ph, R' = Me) are known.²⁹¹ The latter undergoes an unexpected thermal cyclization reaction to yield imidazolones (**173**) (Scheme 27).²⁹²

Tetrazolium ylides are quite reactive and are easily alkylated.¹⁶⁸ The mesoionic tetrazolium thiolate **117** readily adds bromine to yield **174** which can then react with a number of active methylene compounds to give mesoionic compounds, e.g., **175**.^{293,294} They also undergo 1,3-dipolar cycloaddition with olefins and acetylenes to yield bicyclic tetrazolo-thiazolines



Yield 8-49%

Scheme 27



Scheme 28

(176) and tetrazolo-thiazoles (177), respectively (Scheme 28).^{216,295} They react across the S—C—N dipole of hybrid **117a** rather than the N—C—N dipole of hybrid **117b**²¹⁶ commonly seen in other mesoionic compounds.^{297,298} By contrast, the alkylated mesoionic tetrazolium salts react readily with reactive methylene compounds to yield conjugated mesoionic compounds, e.g., **144**.²⁹⁶

The chemistry of tetrazolium thiolates and other mesoionic tetrazoliums has been extensively reviewed.^{297,298} Though there are no reports of the chemical reduction of thiolates to formazan-like structures, the polarographic reduction of the complex betaines (**146**) to formazans has been reported.⁶⁵⁵

7.5. PROPERTIES OF FORMAZANS

The physical and chemical properties of formazans have been reviewed in detail.^{1,2} In this discussion only those properties that directly or indirectly affect the choice of a tetrazolium salt as a leuco dye will be discussed. Spectral, acid—base, redox, and metal complexing properties will be stressed.

7.5.1. Physical Properties

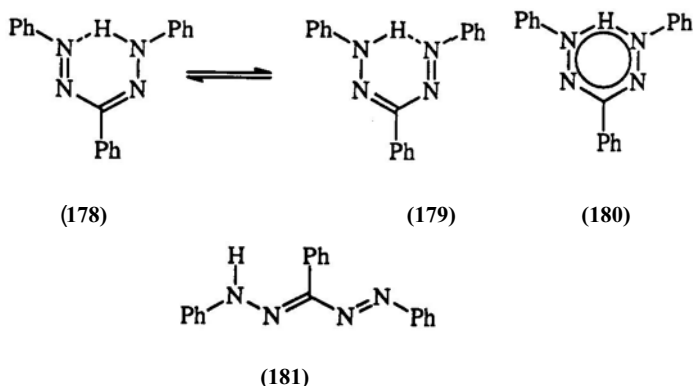
Formazans are solids with relatively low melting points. They have intense colors ranging through most of the visible region. They have negligible water solubility and are generally soluble in common organic solvents. However, when sulfonic, carboxylic, phosphonic acid, or quaternary groups are present, they can become quite water soluble.^{1,299,300}

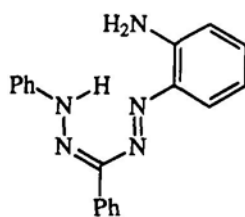
7.5.1.1. Structure

Formazans can be characterized as tautomeric structures **178** and **179**. Schiele proposed that, in some cases at least, formazans are better represented by the delocalized structure **180** implying coplanarity among substituents.^{301,302}

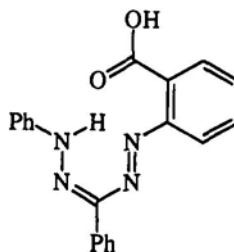
1,3,5-Triphenylformazan can be isolated in two forms; the red form is assigned to the tautomeric structure **178** or **179** and the yellow form is assigned to the trans-anti geometry **181**.^{303,304} This assignment is supported by IR, NMR, X-ray diffraction as well as kinetic studies.^{245,305–315}

Unsymmetrically substituted formazans form a complex mixture of valence tautomers and geometric isomers with different conformations. The tautomerism is further complicated when substituents on the aryl ring are

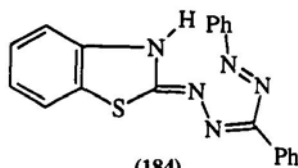




(182)



(183)

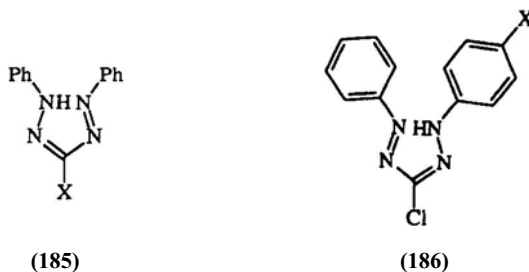


(184)

capable of either deprotonation or hydrogen bonding. Thus, in the case of 1-(2-aminophenyl)-3,5-diphenyl formazan (**182**), using proton and carbon-13 NMR as well as electronic and IR spectra, Ostrovskaya and colleagues proposed a complex equilibrium mixture of six isomers.³¹⁶ Equally complex equilibria arise from the introduction of a carboxylic group in the *ortho* position of the 1-aryl substituent, e.g., **183**.^{317,318} For formazans, containing a heterocyclic ring at the 1-position, e.g., the benzothiazolyl formazan (**184**), a total of nine geometric isomers are possible.^{319–324}

7.5.1.2. Electronic Spectra

Absorption spectra of formazans have been studied in detail. Almost all formazans exhibit UV/visible spectra between 300 and 600 nm.^{1,2,12,13,40,62,325,326} The absorption maxima are very sensitive to substituent effects. For example, the 1,5-diphenyl formazan **185** when X is hydrogen, methyl, phenyl, cyano, and mercapto shows a band at 420, 410, 470, 504, and 590nm in ethanol, respectively. The 3-chloro derivative **186** when X is hydrogen, iodine, bromine, chlorine, and fluorine has a band at 433,433,430,421, and 417 nm, respectively. Table 13 shows the influence of substituents on the absorption maxima in the trisubstituted formazans **3**. Table 14 shows the influence of substituents on the absorption maxima of



a number of 1-(2-benzothiazolyl)-substituted 3,5-diaryl formazans **187**.²⁸³ A plot of the absorption frequencies of the formazan dyes versus the Hammett sigma values of the substituent on the 3-aryl ring is linear; a similar plot for the 5-aryl ring results in a parabolic-shaped curve with a peak at a sigma value of zero hydrogen. Similar results are observed with other heterocyclic formazans.^{231,319 - 324,331}

Table 13. Absorption Maxima of Substituted Formazan (3)

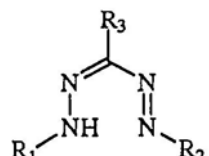
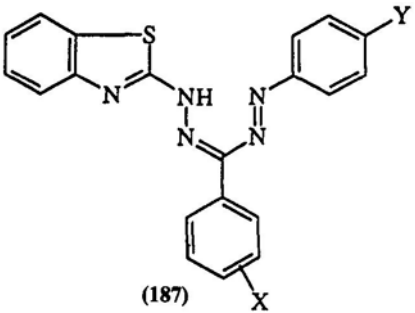
 (3)			
R ₁	R ₃	R ₂	λ _{max} (nm)
Ph	H	Ph	260,285,420
Ph	CH ₃	Ph	260,410
Ph	<i>n</i> -C ₁₁ H ₂₂ -	4-NO ₂ -C ₆ H ₄	427
Ph	Ph	Ph	405
Ph	Ph	α-Naphthyl	275,520
Ph	Ph	β-Naphthyl	270,305,505
Ph	Ph	4-Biphenyl	410
Ph	4-Biphenyl	Ph	320,500
4-Biphenyl	Ph	4-Biphenyl	435
Ph	Ph	4-Cl-C ₆ H ₄	290,410
Ph	Ph	4-I-C ₆ H ₄	500
4-I-C ₆ H ₄	Ph	4-I-C ₆ H ₄	510
α-Naphthyl	Ph	4-NO ₂ -C ₆ H ₄	290,365,438
4-NO ₂ -C ₆ H ₄	Ph	4-I-C ₆ H ₄	500

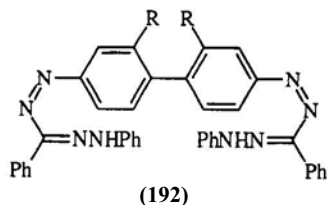
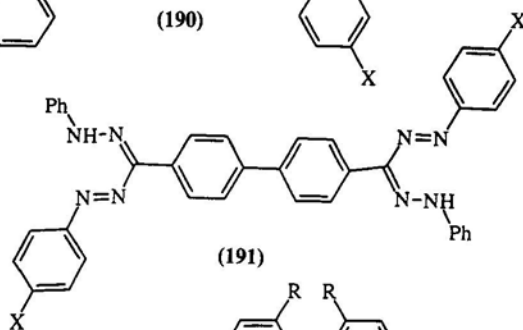
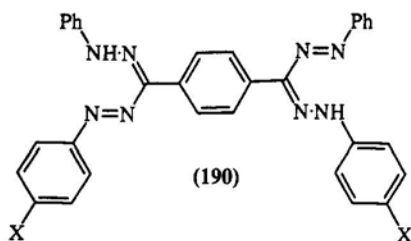
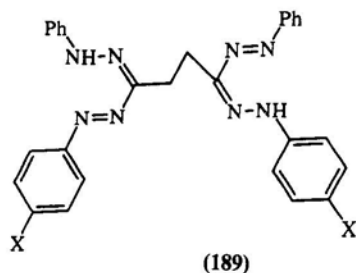
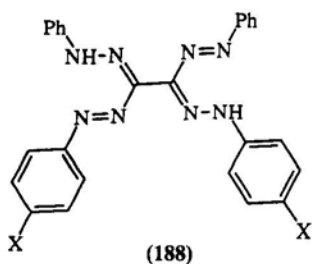
Table 14. Absorption Maxima of Substituted Formazan (**187**)



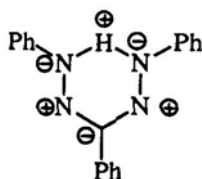
(187)

X	Y	λ_{CHCl_3}	λ_{DMF}
H	H	416	539
4-NO ₂	H	542	623
4-Cl	H	563	632
4-CH ₃	H	578	640
4-OCH ₃	H	584	646
4-Br	H	562	635
3-Br	H	555	630
3-OCH ₃	H	564	640
3-NO ₂	H	546	623
2-NO ₂	H	492	626
2-Cl	H	456	630
2-CH ₃	H	451	637
2-OCH ₃	H	454	642
H	NO ₂	570	563
H	Cl	484	550
H	CH ₃	416	537
H	OCH ₃	416	537
H	CF ₃	535	560
H	CN	554	584
H	N(CH ₃) ₂	514	514
			555 (DMF/NaOH)

Bis-1,5-diaryl formazans generally absorb at longer wavelengths than mono formazans. The absorption maxima depend on the linking group. Formazans **188**—**191** (X = H) absorb at 485, 470, 520, and 572 nm, respectively. The absorption maxima are also influenced by substituents. The formazan **190** (X = CO₂Et) absorbs at 510 nm whereas **191** (X = Me, OMe) absorbs at 585 and 606 nm, respectively.^{12,13} The absorption maximum of **192** shifts from 572 (R = H) to 585 and 602 nm (R = Me, OMe), respec-



tively.³²⁷ The substituent effects are explained on the basis of a pseudo-aromatic structure **193** with alternating polarity.^{197,328} Hückel molecular orbital calculations of the electron densities on the five atoms in symmetrically substituted formazans support this view.³²⁹ The agreement is not satisfactory for unsymmetrically substituted formazans.³³⁰ The electronic spectra of formazans have been the subject of molecular orbital calculations using the LCAO method³³¹ and the SCF method.³³² The latter method has been extended to study the thermal and electronic conductance properties of 1,5-diphenyl-3-cyanoformazan.³³³ Bond distances calculated using the PPP method correlate well with X-ray data.³¹⁵



(193)

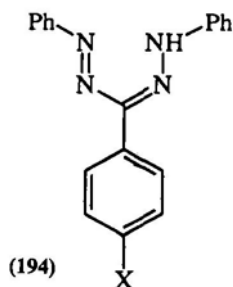
The spectral absorptions shift to longer wavelengths as the solvent polarity increases. However, care must be taken to distinguish them from the spectral shifts due to deprotonation.

7.5.2. Chemical Properties

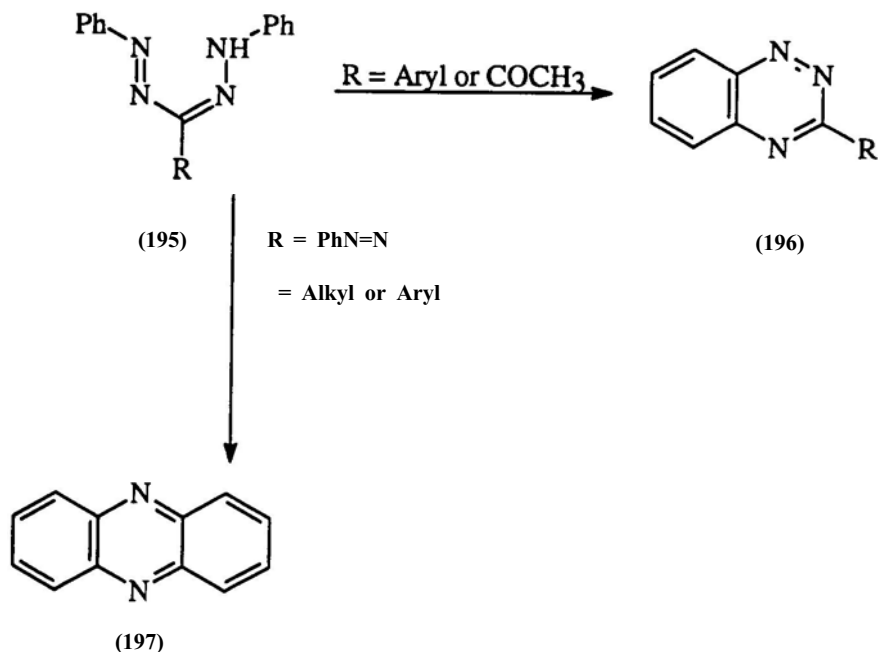
7.5.2.1. Acid—Base Properties

Formazans behave as weak acids as well as weak bases. Salts of formazans have been isolated.^{26,334,335} The acid dissociation constants of some substituted formazans have been determined from their solution spectra.³³⁶

Though formazans can be protonated, there are no reports of isolation of formazan cations. The study of the basicity of formazans is complicated by the fact that exposure to acid can lead to irreversible chemical changes. Recently, the protonation of the triaryl formazan **194** with perchloric acid in aprotic solvents has been studied spectroscopically. In this a hypsochromic shift is observed and is more pronounced when X is an electron-donating substituent. Thus, the shift is 33, 14, and 73nm when X is hydrogen, *p*-methoxy, and *m*-nitro, respectively.³³⁷



(194)



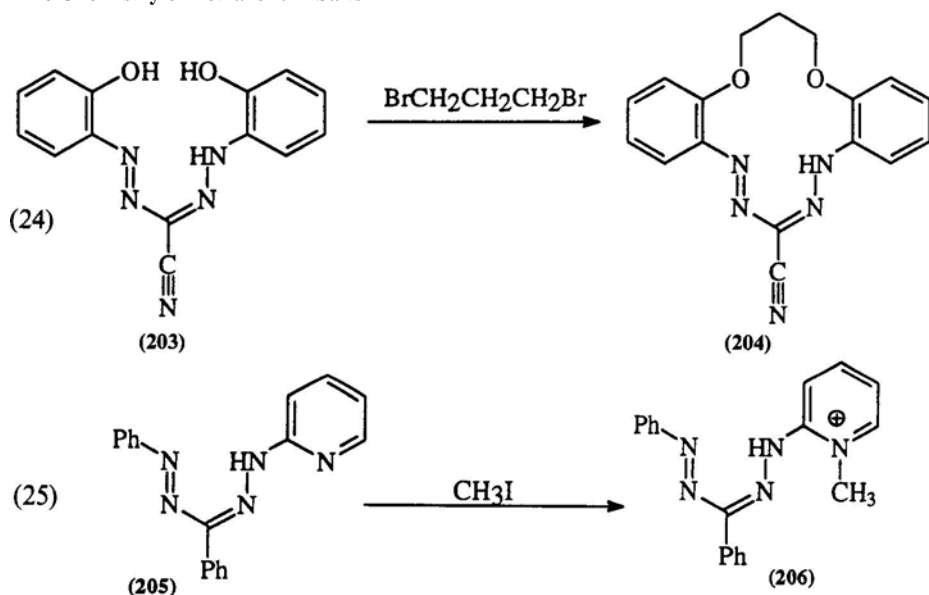
Scheme 29

7.5.2.2. Reaction with Acids

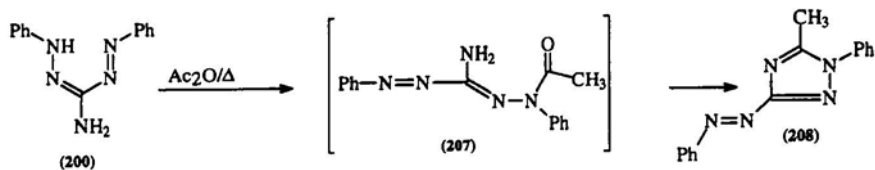
In warm mineral acid, formazans (195) rearrange to a benzotriazine (196) eliminating an amine (Scheme 29).^{8,26,27,334,338,339} However, when R is methyl, phenylazo, or oxalyl, the main product is the phenazine 197 along with a trace amount of the benzotriazine.³⁴⁰ The mechanism of this reaction is not well understood.^{341–345}

7.5.2.3. Reaction with Bases

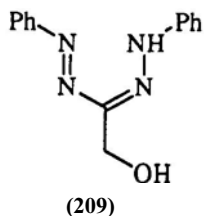
Formazans are stable in alkaline solution. Alkaline hydrolysis of functionalities on formazans such as nitriles, esters, and amides leads to the acids (Section 7.3.1.1). The case of 3-nitroformazans (198) is unique. Reaction with hydroxide ion gives 3-hydroxy formazan (199) which can be readily oxidized to the tetrazolium betaine. In the presence of hydrosulfide, a reduction of the nitro group takes place giving 3-aminoformazan (200) with traces of the 3-mercaptoformazan (201), which by contrast is the main product when ammonium polysulfide is used (Scheme 30).^{45,346}

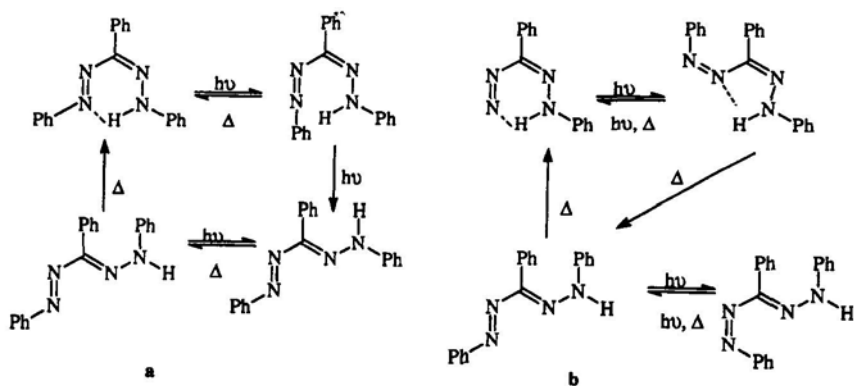


plished with acetic anhydride in the presence of zinc chloride.^{13,21,27,33,34} 2-Amino-1,5-diphenylformazan (**200**) is also resistant to acylation with acetic anhydride under mild conditions; however, on heating, the tetrazole (**208**) is obtained, through acylation of the hydrazo nitrogen (**207**) (Scheme 32).²⁸ By contrast *C*-hydroxyalkyl formazans (**209**) react with acetic anhydride to form the expected *O*-acetyl derivative.³⁵¹



Scheme 32





Scheme 33

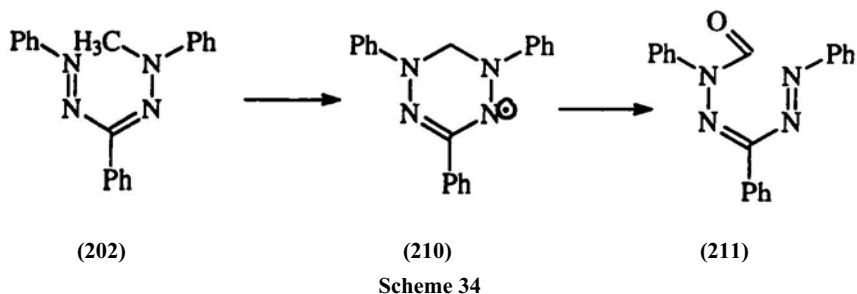
7.5.2.5. Action of Light

It has been recognized early that the red and yellow forms of triphenylformazan are interconvertible under the influence of light.^{262,352} Using spectroscopic, flash photolytic, and kinetic methods, the mechanism of the photochemical and thermal interconversion reactions between the various geometric isomers and conformers has been studied (Scheme 33a,b).^{245,342} However, the exact mechanism is not clear, the data supporting both pathways **a** and **b**.^{353–357,657} Under the influence of UV radiation, triphenylformazan behaves similarly to the corresponding tetrazolium salt yielding the bicyclic tetrazolopyridazinium salt (**152**) through photooxidation.³⁵⁴

7.5.2.6. Oxidation

As one of the main synthetic routes to tetrazolium salts, the oxidation of formazans has been discussed in Section 7.3.1.5. Strong oxidizing agents such as concentrated nitric acid and singlet oxygen (produced chemically or with a sensitizer of low triplet energy such as methylene blue) can lead to degradation to benzoic acid, phenol, and benzene and have no synthetic utility. When a sensitizer with high triplet energy, such as Eosin Y, is used, the expected tetrazolium salt can be isolated.³⁵⁸

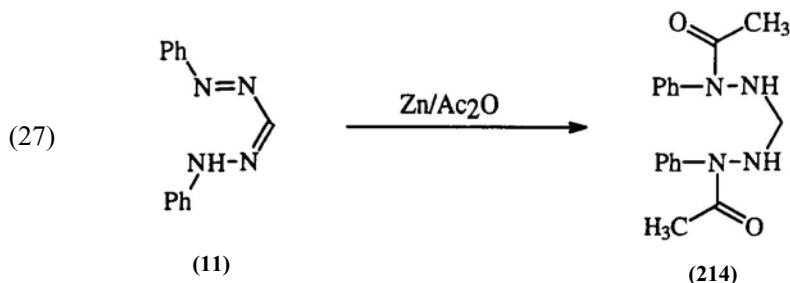
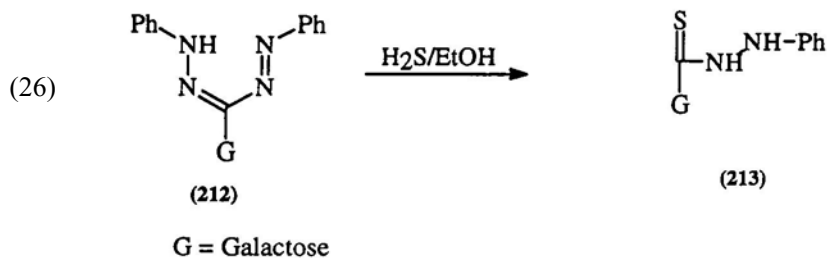
Verdrazyls, e.g., **210**, are a class of cyclic free radicals, with characteristic ESR spectra and intense colors. They represent a special case of “oxidation” of formazans and can be obtained from the methylation of and simultaneous or subsequent dehydrogenation of formazans.^{359–361} Ver-



drazyls can undergo further oxidation to formyl formazans, e.g., **211** (Scheme 34). Polymers containing stable verdrazyl radicals have been prepared and suggested as potential semiconductors^{362,363}

7.5.2.7. Reduction of Formazans

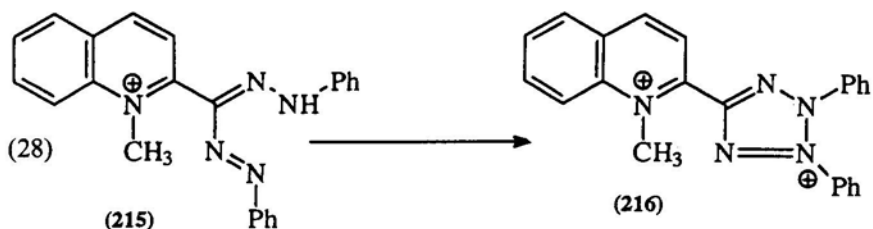
As discussed in Section 7.4.2.5, the reduction of tetrazolium salts to formazans often results in further reduction products. As seen in Scheme 24, reduction of formazans with ammonium sulfide leads to the hydrazidine **161**. The reduction can proceed further eliminating an arylamine, yielding an amidrazone, e.g., **162**.³⁶⁴ By contrast, alcoholic hydrogen sulfide attacks



sugar formazans e.g., **212**, to form the thiogalactonic acid phenylhydrazone (**213**) (Eq. 26).³⁶⁵ Zinc and dilute acids reduce symmetric and unsymmetric formazans to a mixture of a hydrazine and acyl hydrazides.^{318,323,348,366,367} Zinc and acetic anhydride lead cleanly to a diacetylhydrazidine, e.g., **214** (Eq. 27)¹⁰; by contrast, zinc dust in dilute acids leads to degradative reduction with no identifiable products.⁸

7.5.2.8. Electrochemical Oxidation and Reduction

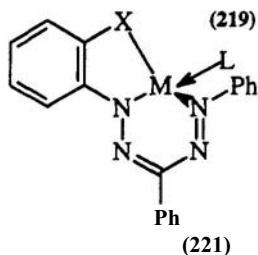
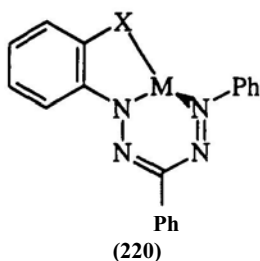
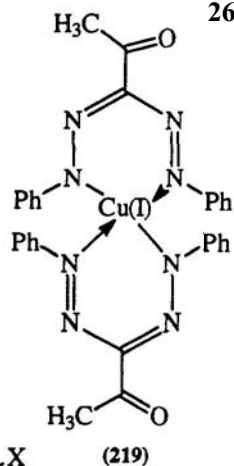
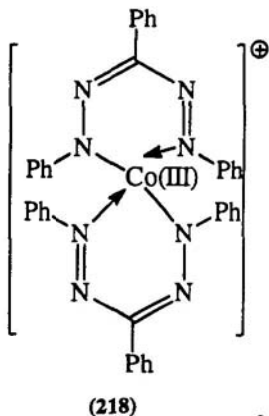
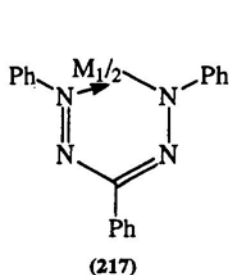
A few electrochemical reductions of formazans to hydrazidine have been reported.^{370,372} However, as discussed in Section 7.4.2.6, electrochemical techniques have been widely used to study the redox chemistry of tetrazolium salts and formazans. Opinions about the reversibility of the electron transfer step, the number of electrons involved, and the identity of the rate-determining step differ widely.^{369–371,656} The electrochemical oxidation of some novel formazans, e.g., **215** produces the dicationic species **216** (Eq. 28). The mechanism is not clearly understood.^{372,373}



7.5.2.9. Metal Complexation

The coordination chemistry of formazan dyes has been extensively reviewed in Venkataraman's classic treatise on synthetic dyes,^{374,375} and more recently in Wilkinson's treatise on coordination compounds.³⁷⁶

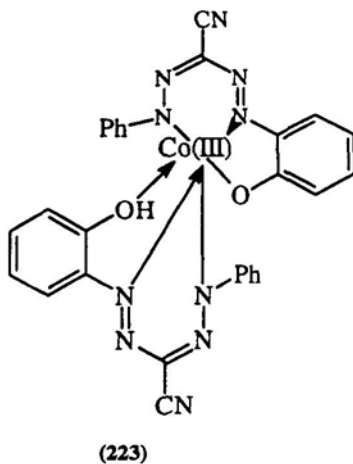
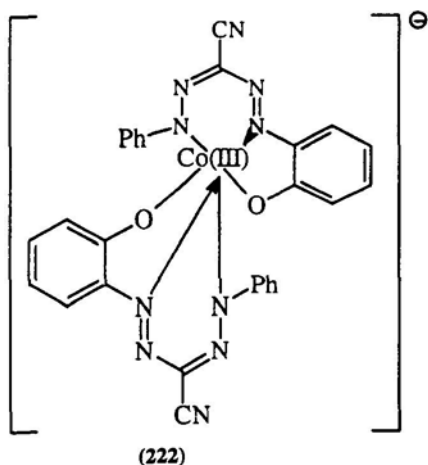
1,3,5-Triphenylformazan behaves as a bidentate ligand forming 2:1 complexes (**217**) with divalent copper, nickel, and cobalt.³⁷⁷ Formazan metal complexes can be compared to complexes of azo dyes or beta diketones due to structural similarity.^{301,302} In general, formazan metal complexes have low stability toward acids. However, when electron-donating substituents are added to the aromatic ring, a considerable enhancement in stability is observed. Cationic complexes of type **218** are also known. The complexation of formazan with metal cation can be accompanied by oxidation to the tetrazolium salt and the formation of a complex

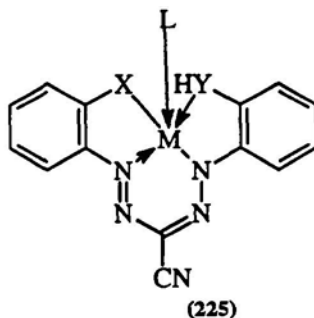
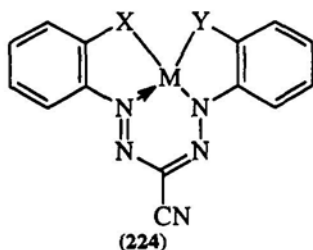


X = O, S, NH, CO₂

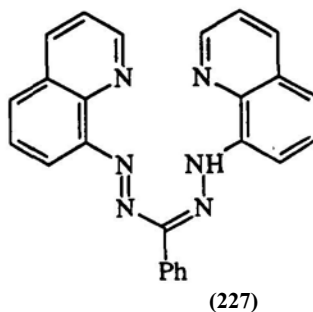
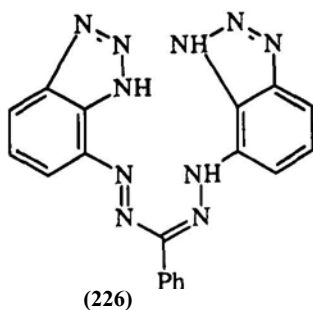
L = H₂O or Pyridine

of a lower valent metal, e.g., **219**.³⁷⁸⁻³⁸³ When the formazans are suitably substituted, they act as tridentate ligands yielding complexes such as **220**, and ligated complexes such as **221**.³⁸⁴⁻³⁸⁶ Tridentate formazans form anionic and neutral 2:1 complexes with trivalent ions, e.g., **222** and **223**.^{380,384,385,387}



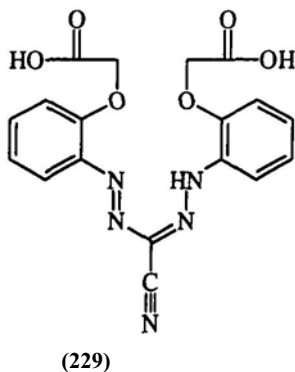
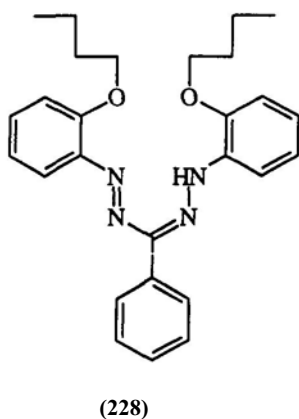


X, Y = O, S, NH or CO₂
L = H₂O or Pyridine



A variety of complexes, e.g., **224** and **225**, can be formed from the tetradentate formazans.^{384,385,388-396} Tetradentate formazans containing heterocycles, e.g., **226** and **227**, also form metal complexes.³⁸⁵

The bulk of the literature on the coordination chemistry of formazans deals with complexes of copper, nickel, cobalt, and chromium.



Other transition metals have received much less attention. Complexes of palladium and 2-amino-phenyl-containing formazans have been reported.³⁹⁷ Mercury complexes of tridentate formazans have been studied.³⁹⁸ Silver complexes of tridentate benzothiazolyl-containing formazans have also been studied.³⁹⁹ Recently, alkali and alkaline earth metals have been the subject of many studies. Formazans such as **228** and **229** as well as the macrocyclic **204** have received considerable attention as metal-specific analytical reagents.^{400–411}

The synthesis and physical properties of these complexes have received much more attention than structure—property relationships. However,

Table 15. Absorption Maxima of Complex **230**

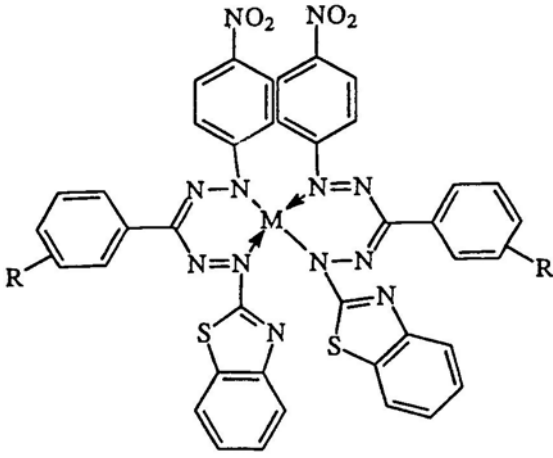
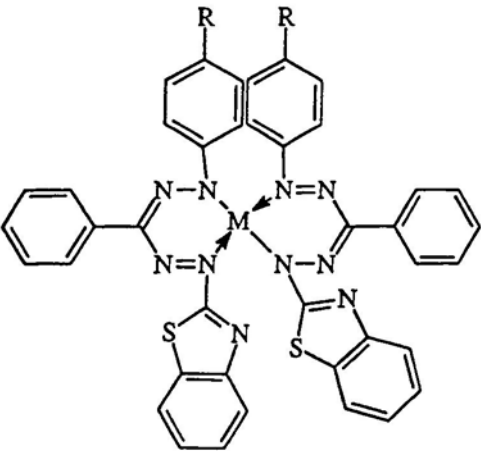
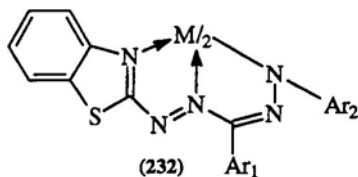
 (230)				
	M			
R	cu	Ni	Co	Zn
H	699	682	670	665
4-OCH ₃	740	701	683	680
4-CH ₃	716	685	675	670
3-OCH ₃	700	671	670	669
4-Cl	695	675	664	660
4-Br	695	677	664	664
3-NO ₂	670	665	654	641
4-NO ₂	665	660	650	640
4-CF ₃	615	660	650	640

Table 16. Absorption Maxima of Complex **231**

 (231)				
M				
R	Cu	Ni	Co	Zn
H	651	642	625	617
N(CH ₃) ₂	712	660	655	650
OCH ₃	663	644	626	620
CH ₃	652	643	622	619
Cl	665	650	634	627
CN	693	667	655	650
NO ₂	699	682	665	660

great interest has been shown regarding the shift in color resulting from complexation.^{283,411-414}

Tables 15 and 16 show the absorption maxima of some metal complexes of benzothiazolyl-substituted formazans **230** and **231**.²⁸³ The wavelengths are metal ion dependent, making formazans useful reagents for the identification of specific metal ions or the simultaneous determination of two ions. The wavelengths are much longer than those of the formazan anion (Table 14). The general trend for electron-rich substituents is toward a larger shift; this is to be expected as it tends to enhance the aromatic character of the ring and increase the covalent character of the metal—nitrogen bond. The sharpness of the absorption band has been attributed to coordination to the heterocyclic nitrogen as in **232**.⁵⁷⁸



The IR bands in a number of nickel complexes of triaryl formazans have been assigned by Arnold and Schiele.⁴¹⁵ A similar assignment of the electronic bands has been carried out.⁴¹⁴ LCAO-MO calculations correlate well with these assignments⁴¹⁷ and have been extended to include both inner ligand transitions as well as charge transfer bands and $d-d$ transitions.⁴¹⁸ EPR spectra have been used to study the nature of bonding in copper complexes of heterocyclic-containing formazans.⁴¹⁹ Metal formazan complexes have also been studied by electrochemistry.^{283,398,420-422}

7.6. APPLICATIONS OF TETRAZOLIUM SALTS

With few exceptions, by far most applications of tetrazolium salts (e.g., analytical, photographic, and biochemical) utilize their reducibility to the corresponding formazan dyes. Tetrazolium salts, due to their resistance to acid and oxidation and the presence of a positive charge, find use in other applications such as antistatic agents and phase transfer catalysts. Over the past two decades, there have been thousands of citations regarding the applications of tetrazolium salts. Most of these citations are patents with similar or overlapping and even identical claims. Any attempt at completeness would be futile. The applications are sorted where discernible, and the earliest or the broadest claims are cited.

7.6.1. Analytical

Most analytical uses of tetrazolium salts utilize their reducibility. The ability of the resulting formazan to coordinate to metal ions, causing a characteristic shift in the spectrum, is often utilized to determine the metal ions or to enhance the sensitivity of the detection.

7.6.1.1. Determination of Reducing Substances

A number of reducing agents have been determined directly using tetrazolium salts. Thus, the analyses of reducing sugars,^{423,424} hydrazides,⁴²⁵ sulfides and thiols,⁴²⁶ ascorbic acid,^{427,428} formaldehyde,⁴²⁹ L-

dopa⁴³⁰ among others have been reported. The method is extended to the analysis of some drugs,^{431—433} antibiotics,⁴³⁴ and pesticides.⁴³⁵ Proteins and nucleic acids⁴³⁸ can be determined indirectly. Enzymatic methods will be discussed in Section 7.6.2.

7.6.1.2. The Determination of Metal Ions

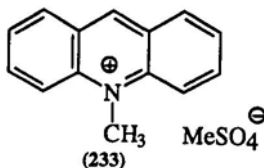
The ability of metal ions to form complexes with formazans is utilized to determine these ions either directly (for low valent reducing ions) or indirectly in the presence of a reducing agent. Among others, molybdenum(VI) and vanadium(V) have been determined using this method.^{442,443} Indirect methods have been reported for the analyses of substances that do not reduce tetrazolium salts. Examples include arsenic in nickel ores⁴³⁶ and traces of selenium.⁴³⁷ A method for the extraction and analysis of a number of metal “ternary ion association complexes” has been described.^{444—448}

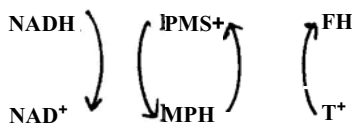
7.6.2. Biochemical

The biological applications of tetrazolium salts are the subject of a textbook.⁹⁶ Kuhn and Jerchel⁷⁴ were the first to recognize the utility of tetrazolium salts as indicators in redox enzyme activity, particularly those of the various dehydrogenases. It has been recognized⁴⁴⁹ that this particular utility of tetrazolium salts is related to the proximity of their redox potentials to those of the hydride transfer systems in biology⁴⁵⁰ such as nicotinamide adenine dinucleotide, NAD, and its phosphate analogue, NADP.

The reduction of tetrazolium salts by NADH is greatly accelerated by electron transfer agents (ETAs) such as phenazine methosulfate (PMS; 233) or its derivatives.^{451—454} Other classes of ETAs such as quinones,^{455,456} ferricinium,⁴⁵⁷ phenothiazine,⁴⁵⁸ the viologens,⁴⁵⁹ acridiniums,⁴⁶⁰ and phenazinium or quinoxalinium salts⁴⁶¹ as well as the enzyme diaphorase⁴⁶² have been used.

The mechanism of this electron transfer has been the subject of many studies. Many workers support the involvement of the superoxide radical ion.^{463—468} However, a recent study⁴⁶⁹ based on EPR⁴⁷⁰ and electrochemi-





MPH = Reduced Phenazinium

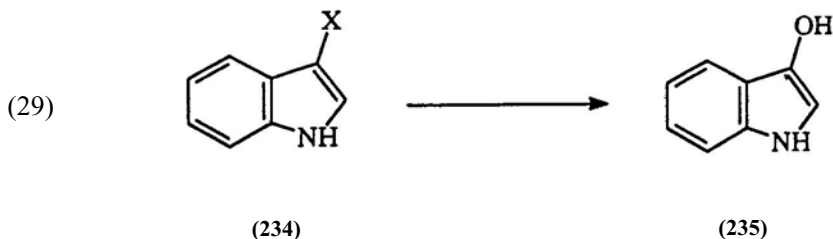
FH = Formazan

T+ = Tetrazolium

Scheme 35

cal data⁴⁷¹ concludes that the superoxide radical, while capable of interacting with both the tetrazolium salt and PMS, is not involved in the redox cycle NADH/tetrazolium (Scheme 35).

Tetrazolium salts are used to follow the reaction of these enzymes or to quantify their substrates/products. Therefore, a variety of tetrazolium salts have been used to study a large number of dehydrogenases.^{439,440,475-491} Other enzymes that generate products that are susceptible to oxidation by dehydrogenases can also be followed with tetrazolium salts.⁴⁹⁴ For example, indoxyl derivatives (**234**) can act as substrates for hydrolytic enzymes such as phosphatase and galactosidase. The resulting indoxyl (**235**) reduces tetrazolium salts to formazans providing a method for the determination of these enzymes (Eq. 29).⁴⁹²⁻⁴⁹⁶ Since redox enzymes, including dehydrogenases, are widely spread in living systems, tetrazolium salts as direct or indirect detectors of these activities have found use in all areas of life sciences; only some aspects of these applications are discussed here.



x = OPO₃H₂

= O-galactopyranosyl

7.6.2.1. Clinical Uses

Levels of a number of metabolites as well as a number of enzymes in body fluids are indicative of disease conditions. Many of the enzymatic reactions mentioned above have been used in solution clinical assays as well as in test strips.^{446,497-508,512-515} Assays for hydrogen peroxide and the enzyme peroxidase using NADH and a tetrazolium salt have been described.^{509,510} Assays of exogenous substances (e.g., drugs or their metabolites) also utilize this chemistry. The determination of alcohol using alcohol dehydrogenase is an example.⁵¹¹ As mentioned above, the assay of enzyme levels can also be achieved using tetrazolium salts.⁵¹⁶⁻⁵²⁰

Tetrazolium salts can be reduced nonselectively by many endogenous reductants such as thiol-containing proteins, as well as exogenous ones such as ascorbic acid.⁵²¹⁻⁵²³ This can lead to serious interferences and several measures have been described to reduce or eliminate their effect.^{524,525,650}

In microbiology, the reduction of tetrazolium salts has been used to detect the presence of microorganisms in serum.⁵²⁶⁻⁵³² The use of tetrazolium salts in hematology has been reviewed.^{533,534} They have been used to measure enhanced phagocytic ability in neutrophils^{535,536} as well as to test for the presence of infectious agents.⁵³⁷⁻⁵⁴¹ They have also been used to evaluate granulocyte function.⁵⁴² Their use has been proposed as a pollen allergy indicator.^{543,545} The reduction of tetrazolium salts by enzymes in living cells is a proposed method to study the chemoselectivity of human tumor cells, the effect of various therapies, and the mode of action of drugs.⁵⁴⁵⁻⁵⁵⁰

7.6.2.2. Nonclinical Uses

Tetrazolium salts have found use in a number of industries both in the detection of bacterial contamination and in process analysis. They are used in meat,⁵⁵¹ fisheries,⁵⁵² milk,^{553,557,558} tanneries,⁵⁵⁴ and the canning industries.^{555,556} Tetrazolium reduction is used to monitor a number of processes in agriculture such as the viability of seed, pollen, yeast, and algae⁵⁵⁹⁻⁵⁶⁷ and to determine the efficacy of herbicides.^{568,544} They also find use as protectors against oxidative degradation in roots⁵⁷⁰ and leaves.⁵⁷¹ The use of tetrazolium salts to measure dehydrogenase activity in sludges has been an important method for the detection of toxic substances.⁵⁷²⁻⁵⁷⁷

7.6.3. Photographic

Wilkinson's treatise on applications of coordination compounds includes a chapter that describes the use of formazan/tetrazolium systems

in both conventional silver halide and nonsilver photographic applications.⁵⁷⁸

7.6.3.1. Silver Halide Photography

Various aspects of silver halide photographic theory and practice are discussed in many textbooks notably the Mees and James series.⁵⁷⁹ Although a three-color system can be designed based on three tetrazolium salts that would lead to yellow, magenta, and cyan formazan dyes, there is only one reference to such a system, involving the use of cyanide ions.⁵⁸⁰ However, the principle is utilized to produce dye-enhanced silver images.^{581,582} The incorporation of tetrazolium salts in the photographic processing solution leads to more rapid processing,^{583,584} which may arise from the tetrazolium salt acting as an electron transfer agent or preventing the buildup of reducing agents.⁵⁸² The acceleration in processing is also seen when the tetrazolium salts are incorporated in the photographic emulsion. This generally leads to high-contrast materials, useful in the production of lithographic plates.⁵⁸⁵⁻⁵⁹⁴ Tetrazolium salts also impart increased stability to these compositions against a number of environmental conditions.⁵⁹⁵⁻⁶⁰⁷

7.6.3.2. Nonsilver Photography

For convenience, the applications of tetrazolium salts to nonsilver photography will be divided into two sections: photochemical systems and photoconductive systems.

Photochemical systems are similar to the silver halide-based systems in that light causes a stoichiometric chemical change (a latent image) which can be amplified (developed) to an image either by heat or by activation by another chemical. Inorganic photosensitive compounds such as ferric, vanadic, or molybdc ions, palladium oxalate and various cobaltic complexes,⁶⁰⁸⁻⁶¹⁰ and organic photosensitive compounds such as quinones,⁶¹¹⁻⁶¹⁵ benzimidazoles,⁶¹⁶ and aziridines⁶¹⁷ are amenable to development using tetrazolium salts.

The principles of photoconductive systems are outlined in many texts, notably Mort and Pai's text,⁶¹⁸ and several chapters of Gregory's text on organic colorants are also useful.⁶¹⁹ Tetrazolium salts are used in electrophotography primarily as toners and charge control agents leading to high-quality images both in black and white and color reproductions.⁶²⁰⁻⁶²⁴

In addition, the photosensitivity of some tetrazolium salts can be used as the basis of an imaging system.⁶²⁵ They have been used with electro-

chromic electrodes in display devices,^{626 - 629} with electropolymerizable resist systems, and with photoelectrolytic cells.^{630 - 633}

7.6.4. Miscellaneous

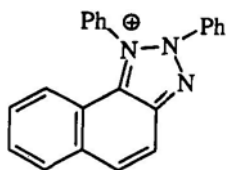
The combination of a positive charge and reducibility of tetrazolium salts finds use as anticorrosion agents for metals.^{634,635} They are components of an oxidant/etchant bath composition for silicon dioxide corrosion-resistant surfaces.⁶³⁶ They are also used as antistatic agents in polyamide yarns.^{637,638}

Tetrazolium salts have found use as phase transfer catalysts in the oxidation of benzaldehyde⁶⁴⁰ and toluene¹⁹³ and the displacement reaction of acid chlorides with sodium azide.⁶³⁹

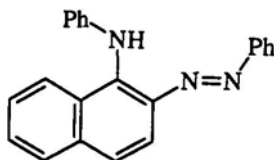
Formazans and their metal complexes are used as textile dyes by direct application. The *in situ* reduction of tetrazolium salts has not been used to introduce the dyes to their substrates. Treatment with triaryl mono and bis tetrazolium salts followed by a reducing agent such as ascorbic acid or thioglycolic acid has been claimed as a method of introducing formazans as permanent hair dyes.⁶⁴¹ There are some references to their use as therapeutic agents.⁶⁴²⁻⁶⁴⁴

7.7. CONCLUSIONS

It is remarkable that more than a century after the discovery of tetrazoliums, they continue to have wide applications. In particular, the reductive ring opening reaction leading to formazans continues to receive a lot of attention. In 1993, there were 316 citations to tetrazolium salts in *Chemical Abstracts*, 23 of which were to their reduction. Yet, the same reaction that makes them a unique class of reduction indicator leuco dyes, may be a part of a broader phenomenon.



(236)



(237)

Recent European patents,^{645,646} drawing on much earlier work⁶⁴⁷⁻⁶⁴⁹ describe an assay for NADH based on its ability to reduce naphthotriazolium salts (**236**) to the azo dye (**237**) in close similarity to tetrazolium salts.

It would seem likely that tetrazolium salts are only one class of a wider variety of redox indicators acting through reductive ring opening, and that many more examples will be discovered in the future that may open some new directions to the chemistry of tetrazolium salts.

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